

# Estimation of parameter sensitivities for stochastic reaction networks using tau-leap simulations

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## Abstract

We consider the important problem of estimating parameter sensitivities for stochastic models of reaction networks that describe the dynamics as a continuous-time Markov process over a discrete lattice. These sensitivity values are useful for understanding network properties, validating their design and identifying the pivotal model parameters. Many methods for sensitivity estimation have been developed, but their computational feasibility suffers from the critical bottleneck of requiring time-consuming Monte Carlo simulations of the exact reaction dynamics. To circumvent this problem one needs to devise methods that speed up the computations while suffering acceptable and quantifiable loss of accuracy. We develop such a method by first deriving a novel integral representation of parameter sensitivity and then demonstrating that this integral may be approximated by any convergent tau-leap method. Our method is easy to implement, works with any tau-leap simulation scheme and its accuracy is proved to be similar to that of the underlying tau-leap scheme. We demonstrate the efficiency of our methods through numerical examples. We also compare our method with the tau-leap versions of certain finite-difference schemes that are commonly used for sensitivity estimations.

**Keywords:** parameter sensitivity; reaction networks; Markov process; tau-leap simulations

**Mathematical Subject Classification (2010):** 60J22; 60J27; 60H35; 65C05.

## 1 Introduction

The study of chemical reaction networks is an essential component of the emerging fields of Systems and Synthetic Biology [1, 45, 16]. Traditionally chemical reaction networks were modeled in the deterministic setting, where the dynamics is represented by a set of ordinary differential equations (ODEs) or partial differential equations (PDEs). In the study of intracellular chemical reactions, some chemical species are present in low copy numbers. Since the behavior of individual molecules is best described by a stochastic process, in the low molecular copy number regime, the copy numbers of the molecular species itself is better modeled by a stochastic process than by ODEs [18]. Only in the limit of large molecular copy numbers, one expects the deterministic models to be accurate [3]. While our work in this paper is focused on biochemical reaction networks as primary examples, we emphasize that the mathematical framework of reaction networks can also be used to describe a wide range of other phenomena in fields such as Epidemiology [27] and Ecology [8].

Suppose  $\theta$  is a parameter (like ambient temperature, cell-volume, ATP concentration etc.) that influences the rate of firing of reactions. Let  $(X_\theta(t))_{t \geq 0}$  be the  $\theta$ -dependent Markov process representing the reaction

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dynamics, and suppose that for some real-valued function  $f$  and observation time  $T$ , our output of interest is  $f(X_\theta(T))$ . This output is a random variable and we are interested in determining the sensitivity of its expectation  $\mathbb{E}(f(X_\theta(T)))$  w.r.t. infinitesimal changes in the parameter  $\theta$ . We define this sensitivity value, denoted by  $S_\theta(f, T)$ , as the partial derivative

$$S_\theta(f, T) := \frac{\partial}{\partial \theta} \mathbb{E}(f(X_\theta(T))). \quad (1.1)$$

Determining these parametric-sensitivity values are useful in many applications, such as, understanding network design and its robustness properties [42], identifying critical reaction components, inferring model parameters [15] and fine-tuning a system’s behavior [14].

Generally the sensitivities of the form (1.1) cannot be directly evaluated, but instead, they need to be estimated with Monte Carlo simulations of the dynamics  $(X_\theta(t))_{t \geq 0}$ . Many methods have been developed for this task [23, 40, 41, 2, 25, 26], but they all rely on exact simulations of  $(X_\theta(t))_{t \geq 0}$  that can be performed using schemes such as Gillespie’s *stochastic simulation algorithm* (SSA) [18]. This severely constrains the computational feasibility of these sensitivity estimation methods because these exact simulations become highly impractical if the rate of occurrence of reactions is high [20], which is typically the case. The main difficulty is that exact simulation schemes keep track of each reaction event which is very time-consuming. To avoid this problem, tau-leaping methods have been developed that proceed by combining many reaction-firings over small time intervals [19] in such a way that insignificant stochastic effects are discarded in favor of computational speed. Tau-leap methods haven been shown to produce good approximations of the reaction dynamics, at a small fraction of the computational cost of exact simulations [19, 11, 36, 44, 5, 39, 38, 31]. Their accuracy has also been investigated theoretically in many papers [37, 30, 6, 35].

Our goal in this paper is to develop a method that leverages the accuracy and computational efficiency of tau-leap methods for the purpose of estimating sensitivity values of the form (1.1). Our method, called *Tau Bernoulli Path Algorithm* ( $\tau$ BPA), works with any underlying tau-leap simulation scheme and it is based on a novel integral representation of parameter sensitivity  $S_\theta(f, T)$  that we derive in this paper. We provide computational examples that show that using  $\tau$ BPA we can often *trade-off* a small amount of bias for large savings in the overall computational costs for sensitivity estimation. We prove that the bias incurred by  $\tau$ BPA depends on the step-size in the same way as the bias of the tau-leap scheme chosen for simulations. Moreover if we substitute the tau-leap simulations in  $\tau$ BPA with the exact SSA generated simulations, then we recover a new unbiased method for sensitivity estimation that is similar to the method in [26]. For the sake of comparison, we also propose the *tau-leap versions* of certain commonly used finite-difference estimators (see [2, 40]) that approximate the infinitesimal derivative in (1.1) by a finite-difference (see (2.9)). Such estimators are computationally faster than  $\tau$ BPA but they suffer from two sources of bias (finite-differencing and tau-leap approximations) unlike  $\tau$ BPA which only incurs bias from the latter source. Our examples indicate that the biases from these two sources often pile on top of each other, making these finite-difference estimators much more inaccurate in comparison to  $\tau$ BPA.

This paper is organized as follows. In Section 2 we formally describe the stochastic model for reaction dynamics and the sensitivity estimation problem. We also discuss the existing sensitivity estimation methods, introduce the tau-leap simulation schemes and explain the rationale for using such simulations in sensitivity estimation. The main results of this paper including the description of our novel tau-leap sensitivity estimation method  $\tau$ BPA is contained in Section 3. In Section 4 we provide computational examples to compare our method with other methods and finally in Section 5 we conclude and provide directions for future research.

## 2 Preliminaries

Consider a reaction network with  $d$  species and  $K$  reactions. We describe its kinetics by a continuous time Markov process whose state at any time is a vector in the non-negative integer orthant  $\mathbb{N}_0^d$  comprising of the molecular counts of all the  $d$  species. The state evolves due to transitions caused by the firing of reactions. We suppose that when the state is  $x$ , the rate of firing of the  $k$ -th reaction is given by the *propensity* function  $\lambda_k(x)$  and the corresponding state-displacement is denoted by the stoichiometric vector  $\zeta_k \in \mathbb{Z}^d$ . There are several ways to represent the Markov process  $(X(t))_{t \geq 0}$  that describes the reaction kinetics under these

assumptions. We can specify the generator (see Chapter 4 in [13]) of this process by the operator

$$\mathbb{A}h(x) = \sum_{k=1}^K \lambda_k(x) (h(x + \zeta_k) - h(x)), \quad (2.2)$$

where  $h$  is any bounded real-valued function on  $\mathbb{N}_0^d$ . Alternatively we can express the Markov process directly by its random time-change representation (see Chapter 7 in [13])

$$X(t) = X(0) + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(X(s)) ds \right) \zeta_k, \quad (2.3)$$

where  $\{Y_k : k = 1, \dots, K\}$  is a family of independent unit rate Poisson processes. Since the process  $(X(t))_{t \geq 0}$  is Markovian, it can be equivalently specified by writing the *Kolmogorov forward equation* for the evolution of its probability distribution  $p_t(x) := \mathbb{P}(X(t) = x)$  at each state  $x$ :

$$\frac{dp_t(x)}{dt} = \sum_{k=1}^K p_t(x - \zeta_k) \lambda_k(y - \zeta_k) - p_t(x) \sum_{k=1}^K \lambda_k(x). \quad (2.4)$$

This set of *coupled* ordinary differential equations (ODEs) is termed as the *Chemical Master Equation* (CME) in the biological literature [3]. As the number of ODEs in this set is typically infinite, the CME is nearly impossible to solve directly, except in very restrictive cases. A common strategy is to estimate its solution using *pathwise* simulations of the process  $(X(t))_{t \geq 0}$  using Monte Carlo schemes such as Gillespie's SSA [18], the *next reaction method* [17], the *modified next reaction method* [4], and so on. While these schemes are easy to implement, they become computationally infeasible for even moderately large networks, because they account for each and every reaction event. To resolve this issue, tau-leaping methods have been developed which will be described in greater detail in Section 2.4.

We now assume that each propensity function  $\lambda_k$  depends on a real-valued system parameter  $\theta$ . To emphasize this dependence we write the rate of firing of the  $k$ -th reaction at state  $x$  as  $\lambda_k(x, \theta)$  instead of  $\lambda_k(x)$ . Let  $(X_\theta(t))_{t \geq 0}$  be the Markov process representing the reaction dynamics with these parameter-dependent propensity functions. As stated in Section 1, for a function  $f : \mathbb{N}_0^d \rightarrow \mathbb{R}$  and an observation time  $T \geq 0$ , our goal is to determine the sensitivity value  $S_\theta(f, T)$  defined by (1.1). This value cannot be computed directly for most examples of interest and so we need to find ways of estimating it using simulations of the process  $(X_\theta(t))_{t \geq 0}$ . Such simulation-based sensitivity estimation methods work by specifying the construction of a random variable  $s_\theta(f, T)$  whose expected value is “close” to the true sensitivity value  $S_\theta(f, T)$ , i.e.

$$S_\theta(f, T) \approx \mathbb{E}(s_\theta(f, T)). \quad (2.5)$$

Once such a construction is available, a large number (say  $N$ ) of independent realizations  $s_1, \dots, s_N$  of this random variable  $s_\theta(f, T)$  are obtained and the sensitivity is estimated by computing their empirical mean  $\hat{\mu}_N$  as

$$\hat{\mu}_N = \frac{1}{N} \sum_{i=1}^N s_i. \quad (2.6)$$

This estimator  $\hat{\mu}_N$  is a random variable with mean and variance

$$\mu_N = \mathbb{E}(\hat{\mu}_N) = \mathbb{E}(s_\theta(f, T)) \quad \text{and} \quad \sigma_N^2 = \text{Var}(\hat{\mu}_N) = \frac{1}{N} \text{Var}(s_\theta(f, T)) \quad (2.7)$$

respectively. For a large sample size  $N$ , the distribution of  $\hat{\mu}_N$  is approximately Gaussian with mean  $\mu_N$  and variance  $\sigma_N^2$ , due to the Central Limit Theorem. The *standard deviation*  $\sigma_N$ , which is the square root of the variance, measures the *statistical spread* of the estimator  $\hat{\mu}_N$ , that is inversely proportional to its *statistical precision*. To safeguard against the possibility of different sample realizations producing very different estimates, the sample size  $N$  must be large enough to ensure that  $\sigma_N$  is small relative to  $\mu_N$ . If

this holds, then  $\hat{\mu}_N$  is a reliable estimator for the true sensitivity value  $S_\theta(f, T)$  because it is very likely to assume a value close to its mean  $\mu_N = \mathbb{E}(s_\theta(f, T))$  which in turn is close to  $S_\theta(f, T)$  (see (2.5)). In practice both  $\mu_N$  and  $\sigma_N$  are unknown, but we can estimate them as  $\mu_N \approx \hat{\mu}_N$  and

$$\sigma_N \approx \hat{\sigma}_N = \frac{1}{\sqrt{N(N-1)}} \sqrt{\sum_{i=1}^N (s_i - \hat{\mu}_N)^2}. \quad (2.8)$$

The performance of any sensitivity estimation method (say  $\mathcal{X}$ ) depends on the following three key metrics that are based on the properties of random variable  $s_\theta(f, T)$ :

1. The *bias*  $\mathcal{B}(\mathcal{X}) = \mathbb{E}(s_\theta(f, T)) - S_\theta(f, T)$ , which is the error incurred by the approximation (2.5).
2. The *variance*  $\mathcal{V}(\mathcal{X}) = \text{Var}(s_\theta(f, T))$  of random variable  $s_\theta(f, T)$ .
3. The *computational cost*  $\mathcal{C}(\mathcal{X})$  of generating one sample of  $s_\theta(f, T)$

The bias  $\mathcal{B}(\mathcal{X})$  can be positive or negative, and its absolute value  $|\mathcal{B}(\mathcal{X})|$  can be seen as the upper-bound on the statistical accuracy that can be achieved with method  $\mathcal{X}$  by increasing the sample size  $N$  [9]. As mentioned before, the square-root of the variance  $\mathcal{V}(\mathcal{X})$  measures the statistical precision of the method  $\mathcal{X}$  which determines the number of samples  $N$  that is needed to produce a reliable estimate. The computational cost  $\mathcal{C}(\mathcal{X})$  is the CPU time required for constructing one realization of  $s_\theta(f, T)$ , and hence the total cost of the estimation procedure with  $N$  samples is  $N\mathcal{C}(\mathcal{X})$ . The goal of a good estimation method is to simultaneously minimize the three quantities  $|\mathcal{B}(\mathcal{X})|$ ,  $\mathcal{V}(\mathcal{X})$  and  $\mathcal{C}(\mathcal{X})$ . This creates various conflicts and trade-offs among the existing sensitivity estimation methods as we now discuss.

## 2.1 Biased methods

A sensitivity estimation method  $\mathcal{X}$  is called *biased* if  $\mathcal{B}(\mathcal{X}) \neq 0$ . The most commonly used biased methods are the *finite-difference schemes* which approximate the infinitesimal derivative in the definition of parameter sensitivity (see (1.1)) by a finite-difference of the form

$$S_{\theta,h}(f, T) = \frac{\mathbb{E}(f(X_{\theta+h}(T)) - f(X_\theta(T)))}{h}, \quad (2.9)$$

for a small perturbation  $h$ . The processes  $X_\theta$  and  $X_{\theta+h}$  represent the Markovian reaction dynamics with values of the sensitive parameter set to  $\theta$  and  $\theta + h$  respectively. These two processes can be simulated independently [23] but it is generally better to couple them in order to reduce the variance of the associated estimator. We briefly review two such coupling strategies called *Common Reaction Paths* (CRP) [40] and *Coupled Finite Differences* (CFD) [2].

Replacing each  $\lambda_k(\cdot)$  by  $\lambda_k(\cdot, \theta)$  in (2.3) we obtain the random time-change representation of the  $\theta$ -dependent process  $X_\theta$  as

$$X_\theta(t) = x_0 + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) ds \right) \zeta_k, \quad (2.10)$$

where  $x_0$  is the initial state and  $\{Y_k : k = 1, \dots, K\}$  is a family of independent unit rate Poisson processes. Here each  $Y_k$  captures the intermittency in the firing times of reaction  $k$ . One can regard  $Y_k$  as specifying the *reaction path* for the  $k$ -th reaction. In CRP, the process  $X_{\theta+h}$  is coupled to process  $X_\theta$  by assigning it the same reaction path for each reaction. In other words, the random time-change representation  $X_{\theta+h}$  is given by

$$X_{\theta+h}(t) = x_0 + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(X_{\theta+h}(s), \theta + h) ds \right) \zeta_k, \quad (2.11)$$

where the  $Y_k$ -s are the same as in (2.10). In CFD, the processes  $X_\theta$  and  $X_{\theta+h}$  are also coupled by their random time-change representations, in such a way that they share many common reactions. This is achieved using the split-coupling defined as

$$\begin{aligned} X_\theta(t) = & x_0 + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) \wedge \lambda_k(X_{\theta+h}(s), \theta + h) ds \right) \zeta_k \\ & + \sum_{k=1}^K Y_k^{(1)} \left( \int_0^t [\lambda_k(X_\theta(s), \theta) - \lambda_k(X_\theta(s), \theta) \wedge \lambda_k(X_{\theta+h}(s), \theta + h)] ds \right) \zeta_k \end{aligned} \quad (2.12)$$

$$\begin{aligned} \text{and } X_{\theta+h}(t) = & x_0 + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(X_\theta(s), \theta) \wedge \lambda_k(X_{\theta+h}(s), \theta + h) ds \right) \zeta_k \\ & + \sum_{k=1}^K Y_k^{(2)} \left( \int_0^t [\lambda_k(X_{\theta+h}(s), \theta + h) - \lambda_k(X_\theta(s), \theta) \wedge \lambda_k(X_{\theta+h}(s), \theta + h)] ds \right) \zeta_k, \end{aligned} \quad (2.13)$$

where  $a \wedge b = \min\{a, b\}$  and  $\{Y_k, Y_k^{(1)}, Y_k^{(2)} : k = 1, \dots, K\}$  is again family of independent unit rate Poisson processes.

The finite-difference approximation (2.9) for the true sensitivity value can be expressed as the expectation  $\mathbb{E}(s_{\theta,h}(f, T))$  of the following random variable

$$s_{\theta,h}(f, T) = \frac{f(X_{\theta+h}(T)) - f(X_\theta(T))}{h}.$$

The three metrics (bias, variance and computational cost) based on this random variable define the performance of CRP and CFD. Since both these methods estimate the same quantity  $S_{\theta,h}(f, T)$ , they have the same bias (i.e.  $\mathcal{B}(\text{CRP}) = \mathcal{B}(\text{CFD})$ ). However in many cases it is found that the CFD coupling is *tighter* than the CRP coupling, resulting in a lower variance of  $s_{\theta,h}(f, T)$  (i.e.  $\mathcal{V}(\text{CFD}) < \mathcal{V}(\text{CRP})$ ) (see [2]). For each realization of  $s_{\theta,h}(f, T)$ , both CRP and CFD require simulation of a coupled trajectory  $(X_\theta, X_{\theta+h})$  in the time interval  $[0, T]$ . The computational costs of such a simulation is roughly  $2\mathcal{C}_0$ , where  $\mathcal{C}_0$  is the cost of *exactly* simulating the process  $X_\theta$  using Gillespie's SSA [18] or a similar method.<sup>1</sup>

Finite-difference schemes introduce a bias in the estimate whose size is proportional to the perturbation value  $h$  (i.e.  $\mathcal{B}(\text{CRP}) = \mathcal{B}(\text{CFD}) \propto h$ ), but the constant of proportionality can be quite large in many cases, leading to significant errors even for small values of  $h$  [26]. Unfortunately we cannot circumvent this problem by choosing a very small  $h$  because the variance is proportional to  $1/h$  (i.e.  $\mathcal{V}(\text{CRP}), \mathcal{V}(\text{CFD}) \propto 1/h$ ). Therefore if a very small  $h$  is selected, the variance will be enormous and the sample-size  $N$  required to produce a statistically precise estimate will be very large, imposing a heavy computational burden on the estimation procedure [26]. This trade-off between bias and variance is the main drawback of finite-difference schemes and there does not exist a strategy for selecting  $h$  that optimally balances these two quantities. Note that unlike bias and variance, the computational cost of generating a sample (i.e.  $\mathcal{C}(\text{CRP})$  or  $\mathcal{C}(\text{CFD})$ ) does not change significantly with  $h$ , thereby ensuring that as  $h$  varies, the total computational burden varies linearly with the required number of samples  $N$ .

Apart from finite-difference schemes, there exists another biased method [41] that approximates the sensitivity value (1.1) as

$$\frac{\partial}{\partial \theta} \mathbb{E} \left( \int_{T-w}^{T+w} \frac{1}{2w} f(X_\theta(t)) dt \right),$$

which is obtained by replacing the output  $f(X_\theta(T))$  with its *average* value in the time interval  $[T-w, T+w]$ . Such an averaging is performed to *regularize* the sensitivity value, so that it can be estimated using *pathwise-differentiation*. Here the parameter  $w$  is the half-width of the *regularizing window*. It determines the bias and affects the variance in the same way as parameter  $h$  for finite-difference schemes, which implies that this method also has similar trade-offs as the finite-difference schemes.

<sup>1</sup>In fact the cost of generating a realization of  $s_\theta(f, T)$  is usually smaller for CFD in comparison to CRP (i.e.  $\mathcal{C}(\text{CFD}) < \mathcal{C}(\text{CRP})$ ), because the CFD coupling is such that if  $X_\theta(t) = X_{\theta+h}(t)$  for some  $t < T$ , then this equality will hold for the remaining time-interval  $[t, T]$ , allowing us to directly set  $s_{\theta,h}(f, T) = 0$  without completing the simulation in the interval  $[t, T]$ .

## 2.2 Unbiased methods

A sensitivity estimation method  $\mathcal{X}$  is called *unbiased* if  $\mathcal{B}(\mathcal{X}) = 0$ . The main advantage of unbiased methods is that the estimation can in principle be made as accurate as possible by increasing the sample size  $N$ . The first unbiased method for sensitivity estimation is called the *Likelihood Ratio* (LR) method (or the *Girsanov Transformation* method) [21, 33], which works by estimating the  $\theta$ -derivative of the probability distribution of  $X_\theta$ . The LR method is easy to implement and the computation cost of generating each sample is roughly  $\mathcal{C}_0$  – the cost of *exact* simulation of the process  $X_\theta$ . The main issue with LR is that generally the variance of its associated random variable  $s_\theta(f, T)$  is very large (i.e.  $\mathcal{V}(\text{LR}) \gg 1$ ), as has been observed numerically [26, 2, 25, 40] and also investigated theoretically in a recent paper [46]. Due to this large variance, LR method becomes infeasible for most examples of interest, as the number of samples needed to obtain a statistically precise estimate is very high.

With this in mind, we now discuss a couple of new unbiased methods that are based on an explicit formula for parameter sensitivity (1.1) that we now present. Let  $(X_\theta(t))_{t \geq 0}$  be the Markov process representing reaction dynamics and let  $\sigma_0, \sigma_1, \sigma_2$  denote its successive jump times starting with  $\sigma_0 = 0$ . For any state  $x \in \mathbb{N}_0^d$  and time  $t \geq 0$  define

$$\Psi_\theta(x, f, t) = \mathbb{E}(f(X_\theta(t)) | X_\theta(0) = x), \quad (2.14)$$

which is essentially the image of  $f$  under the Markovian semigroup associated with process  $X_\theta$  at time  $t$ . Let  $\lambda_0(x, \theta) = \sum_{k=1}^K \lambda_k(x, \theta)$  and for any  $k = 1, \dots, K$  define

$$R_\theta(x, f, t, k) = \frac{\partial \lambda_k(x, \theta)}{\partial \theta} \int_0^t (\Psi_\theta(x + \zeta_k, f, s) - \Psi_\theta(x, f, s) - f(x + \zeta_k) + f(x)) e^{-\lambda_0(x, \theta)(t-s)} ds. \quad (2.15)$$

Theorem 2.3 in [25] shows that  $S_\theta(f, T)$  exactly satisfies (2.5) with the random variable  $s_\theta(f, T)$  defined by

$$s_\theta(f, T) = \sum_{k=1}^K \left( \int_0^T \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} (f(X_\theta(t) + \zeta_k) - f(X_\theta(t))) dt + \sum_{i=0: \sigma_i < T}^\infty R_\theta(X_\theta(\sigma_i), f, T - \sigma_i, k) \right). \quad (2.16)$$

Note that  $s_\theta(f, T)$  contains a contribution at each jump time  $\sigma_i$  (before time  $T$ ) of process  $X_\theta$  and this contribution is given by the function  $R_\theta$  which does not have an analytical formula for most examples. Hence in order to use this result for sensitivity estimation, we need to estimate all these contributions using *additional* paths of the process  $X_\theta$ . This is accomplished in [25] using a scheme called *Auxiliary Path Algorithm* (APA) that estimates these quantities in parallel using a small number  $M_0$  of additional paths in such a way that the overall estimate remains unbiased. In comparison to the other unbiased method LR, the computational cost of generating each sample for APA is much higher (i.e.  $\mathcal{C}(\text{APA}) \gg \mathcal{C}(\text{LR})$ ) but at the same time its variance is much lower (i.e.  $\mathcal{V}(\text{APA}) \ll \mathcal{V}(\text{LR})$ ). In [25] many examples are provided where APA outperforms LR, because the benefit of lower variance more than compensates for the disadvantage of higher computational cost per sample.

The main drawback of APA is that it tries to estimate *all* the unknown quantities of the form  $R_\theta(x, f, t, k)$  that appear in (2.16), which is very difficult because their number is proportional to the number of jumps of the process  $X_\theta$  in the time interval  $[0, T]$ , which can be very large even for small networks. In [26] a new method is proposed that overcomes this problem by *randomly selecting* a small number of these quantities and estimating them using additional paths, without introducing a bias in the estimate. This method is called *Poisson Path Algorithm* (PPA) because the selection mechanism is based on the values of certain Poisson random variables that are generated “on the run”. Due to this extra randomness, the sample variance for PPA is generally greater than APA (i.e.  $\mathcal{V}(\text{PPA}) > \mathcal{V}(\text{APA})$ ) but the computational cost for realizing each sample is much lower (i.e.  $\mathcal{C}(\text{PPA}) \ll \mathcal{C}(\text{APA})$ ). Moreover in comparison to APA, PPA is far easier to implement and has lower memory requirements, making it an attractive unbiased method for sensitivity estimation. In [26] it is shown using many examples that for a given level of statistical accuracy, PPA can be more efficient than LR and also the finite-difference schemes CFD and CRP. The computational cost of generating each sample in PPA is roughly  $(2M_0 + 1)\mathcal{C}_0$ , where  $M_0$  is a small number that upper-bounds the expected number of unknown quantities that will be estimated using additional paths. For both APA



and PPA, the parameter  $M_0$  serves as a *trade-off* factor between the computational cost and the variance - as  $M_0$  increases, the cost also increases but the variance decreases. However note that both these methods remain unbiased for any choice of  $M_0$ .

The foregoing trade-off relationships for the existing sensitivity estimation methods are summarized in Table 1.

Type	Method $\mathcal{X}$	Trade-off	Trade-off parameter	Preserved Quantity
Biased	CRP	$\mathcal{B}(\mathcal{X}) \quad \& \quad \mathcal{V}(\mathcal{X})$	$h$	$\mathcal{C}(\mathcal{X}) \approx 2\mathcal{C}_0$
	CFD		$h$	
	PD		$w$	
Unbiased	APA PPA	$\mathcal{V}(\mathcal{X}) \quad \& \quad \mathcal{C}(\mathcal{X})$	$M_0$	$\mathcal{B}(\mathcal{X}) = 0$

Table 1: Trade-off relationships among the bias  $\mathcal{B}(\mathcal{X})$ , variance  $\mathcal{V}(\mathcal{X})$  and the computational cost  $\mathcal{C}(\mathcal{X})$  for existing sensitivity estimation methods. Here  $h$  is the perturbation size for finite-difference schemes [2, 40],  $w$  is the regularization half-width for the pathwise differentiation method [41] and  $M_0$  quantifies the number of auxiliary paths for APA [25] and PPA [26]. The cost of *exactly* simulating the underlying process is  $\mathcal{C}_0$ .

### 2.3 Rationale for using tau-leap schemes for sensitivity estimation

All the existing sensitivity estimation methods suffer from a critical bottleneck – they are all based on exact simulations of the process  $X_\theta$ . The computational cost  $\mathcal{C}_0$  of generating each trajectory of  $X_\theta$  can be exorbitant even for moderately large networks and especially those networks that have reactions firing at multiple timescales [47, 12, 10]. One way to counter this problem is to develop methods that can accurately estimate parameter sensitivities with *approximate* computationally inexpensive simulations of the process  $X_\theta$  obtained with tau-leap methods [19, 11]. The use of tau-leap simulations provides a natural way to trade-off a small amount of error with a *potentially* large reduction in the computational costs. This has already been realized in several papers in the context of estimating expectations of the form  $\mathbb{E}(f(X_\theta(T)))$  [11, 36, 31].

Our goal in this paper is to develop a method that can accurately estimate parameter sensitivity  $S_\theta(f, T)$  of the form (1.1) using only tau-leap simulations of the process  $X_\theta$ . This can be done by specifying a random variable  $s_\theta^{(\tau)}(f, T)$  which can be constructed with these tau-leap simulations and whose expected value is “close” to the true sensitivity value  $S_\theta(f, T)$ , i.e.

$$S_\theta(f, T) \approx \mathbb{E}(s_\theta^{(\tau)}(f, T)). \quad (2.17)$$

We propose such a random variable  $s_\theta^{(\tau)}(f, T)$ , by adding “extra randomness” to the random variable  $s_\theta(f, T)$  given by (2.16), and then substituting the exact states of process  $X_\theta$  with the approximate states computed with a tau-leap scheme. We provide a simple algorithm for generating the realizations of  $s_\theta^{(\tau)}(f, T)$ , and we theoretically show that under certain reasonable conditions, the associated estimator is *tau-convergent*, which means that the *bias* incurred due to the approximation in (2.5) converges to 0, as the maximum step-size  $\tau_{\max}$  or the *coarseness* of the time-discretization mesh goes to 0. Hence by making this mesh finer and finer, we can make the estimator as accurate as we desire, provided that we are willing to bear the increasing computational costs. In the context of estimating expected values  $\mathbb{E}(f(X_\theta(T)))$ , the property of tau-convergence along with the rate of convergence, has already been established for many tau-leap schemes [30, 6, 37, 35]. We use these preexisting results and obtain a similar tau-convergence result for our sensitivity estimation method. An important feature of our approach is that it is completely flexible, as far as the choice of the tau-leap simulation method is concerned. Furthermore the order of accuracy of our sensitivity estimation method is the same as the order of accuracy of the underlying tau-leap method.

We end this section with the observations that incorporating tau-leap schemes in sensitivity estimation opens up a new dimension in attacking this challenging problem. Recall the trade-off relationships among the existing sensitivity estimation methods from Table 1. In these methods, parameters like  $h$ ,  $w$  and  $M_0$  only allow us to explore one trade-off curve between the variance  $\mathcal{V}(\mathcal{X})$  and some other metric like the bias  $\mathcal{B}(\mathcal{X})$  (for  $\mathcal{X} = \text{CRP, CFD, PD}$ ) or the computational cost  $\mathcal{C}(\mathcal{X})$  (for  $\mathcal{X} = \text{APA, PPA}$ ). The main

advantage of employing tau-leap schemes is that they provide a mechanism for exploring another trade-off curve between the bias  $\mathcal{B}(\mathcal{X})$  and the computational cost  $\mathcal{C}(\mathcal{X})$ , for the purpose of optimizing the performance of a sensitivity estimation method. Indeed in Section 4, we provide numerical examples to show that with tau-leap simulations we can *indeed* trade-off a small amount of bias with large savings in the computational effort required for estimating parameter sensitivity. Moreover this trade-off relationship is “orthogonal” to existing trade-off relationships mentioned in Table 1 because replacing exact simulations in a sensitivity estimation method, with approximate tau-leap simulations, usually does not alter the variance  $\mathcal{V}(\mathcal{X})$  significantly (see Section 4). Of course, the computational advantage of tau-leap schemes can only be appropriated if we can incorporate them into existing sensitivity estimation methods. The main contribution of this paper is to develop a method, similar to PPA, that works well with tau-leap schemes (see Section 3). For the sake of comparison, we also provide tau-leap versions of the finite-difference schemes (CRP and CFD) in Section 4.

## 2.4 A generic tau-leap method

We now describe a generic tau-leap method that can approximately simulate the stochastic reaction paths defined by the Markov process  $(X(x_0, t))_{t \geq 0}$  with generator  $\mathbb{A}$  (see (2.2)) and initial state  $x_0$ . For each reaction  $k = 1, \dots, K$ , let  $R_k(t)$  be the number of firings of reaction  $k$  until time  $t$ . Due to (2.3) we can express each  $R_k(t)$  as

$$R_k(t) = Y_k \left( \int_0^t \lambda_k(X(x_0, s)) ds \right) \zeta_k,$$

where  $\{Y_k : k = 1, \dots, K\}$  is a family of independent unit rate Poisson processes. From now on we refer to  $R(t) = (R_1(t), \dots, R_K(t))$  as the reaction count vector. For any two time values  $s, t \geq 0$  (with  $s < t$ ), the states at these times satisfy

$$X(x_0, t) = X(x_0, s) + \sum_{k=1}^K (R_k(t) - R_k(s)) \zeta_k.$$

At any given time  $t$  and the computed (approximate) state  $x$  at time  $t$ , a tau-leap method entails taking a predetermined (random) step of size  $\tau > 0$ , based on the information available at time  $t$ , and then generating a sample from an approximating distribution for the state at time  $(t + \tau)$ . This distribution is generally found by approximating the difference  $(R(t + \tau) - R(t))$  in the reaction count vector by a random variable  $\tilde{R} = (\tilde{R}_1, \dots, \tilde{R}_K)$  whose probability distribution is easy to sample from. The most straightforward choice is given by the simple (explicit) Euler method [19], which assumes that the propensities are approximately constant in the time interval  $[t, t + \tau)$  and conditioned on the information at time  $t$ , each  $\tilde{R}_k$  is an independent Poisson random variable with rate  $\lambda_k(x)\tau$ . Other distributions for  $\tilde{R} = (\tilde{R}_1, \dots, \tilde{R}_K)$  have also been used in the literature to obtain better approximations and particularly to prevent the state-components from becoming negative [44]. The selection method for step size  $\tau$  also varies, with the simplest being steps based on a deterministic mesh  $0 = t_0 < t_1 < \dots < t_n = T$  over the observation time interval  $[0, T]$ . To obtain better accuracy several strategies have been proposed that randomly select  $\tau$  based on some criteria such as avoidance of negative state-components or constancy of conditional propensities [11, 5, 31]. There also exist *implicit* tau-leap schemes that can deal with *stiff* systems in an efficient way [36].

To represent a generic tau-leap method we shall use a pair of abstract labels  $\alpha$  and  $\beta$ , where  $\alpha$  denotes a method, i.e. a choice of distribution for  $\tilde{R}$ , and  $\beta$  denotes a step size selection strategy. We will use  $|\beta|$  as a (deterministic) parameter which quantifies the *coarseness* of the time-discretization scheme  $\beta$ . For instance  $\alpha$  may stand for the explicit Euler tau-leap method [19] and  $\beta$  may stand for a deterministic mesh  $0 = t_0 < t_1 < \dots < t_n = T$ , and in this case the coarseness parameter is  $|\beta| = \max(t_j - t_{j-1})$ . Typically, tau-leap methods produce approximations of the underlying process at certain leap times that are separated by the step-size  $\tau$  and one can interpolate these approximate state values at other time points. The most obvious interpolation is the “sample and hold” method, where the tau-leap process is held constant between the consecutive leap times. In circumstances, such as the explicit Euler tau-leap method with Poisson updates, it is more natural to use interpolation strategies based on the random time-change representation (2.3) – for example see the “Poisson bridge” approach in [28]. In the following discussion, we suppose that



the interpolation strategy is also determined by the label  $\alpha$ . We shall use  $(Z_{\alpha,\beta}(x_0, t))_{t \geq 0}$  to denote the tau-leap process, that approximates the exact dynamics  $(X(x_0, t))_{t \geq 0}$ , and that results from the application of a tau-leap method  $\alpha$  with step size selection strategy  $\beta$ . This process is defined by the prescription

$$Z_{\alpha,\beta}(x_0, t_0) = x_0 \quad \text{and} \quad Z_{\alpha,\beta}(x_0, t_{i+1}) = Z_{\alpha,\beta}(x_0, t_i) + \sum_{k=1}^K \zeta_k \tilde{R}_{k,i,\alpha,\beta} \quad \text{for } i = 1, \dots, \mu, \quad (2.18)$$

where  $\mu$  is the (possibly) random number of time points,  $0 = t_0 < t_1 < \dots < t_\mu = T$  are the (possibly) random leap times, and  $\tilde{R}_{k,i,\alpha,\beta}$  for  $i = 1, \dots, \mu$  and  $k = 1, \dots, K$  are random variables whose distribution when conditioned on  $Z_{\alpha,\beta}(x, t_i)$  is determined by the method  $\alpha$  and step size strategy  $\beta$ .

**Remark 2.1** *Note that this generic tau-leap method reduces to Gillespie's SSA [18], if at state  $Z_{\alpha,\beta}(x_0, t_i) = z$ , the next step size  $\tau$  is an exponentially distributed random variable with rate  $\lambda_0(z) := \sum_{k=1}^K \lambda_k(z)$  and each  $\tilde{R}_{k,i,\alpha,\beta}$  is chosen as*

$$\tilde{R}_{k,i,\alpha,\beta} = \begin{cases} 1 & \text{if } k = \eta \\ 0 & \text{otherwise,} \end{cases}$$

where  $\eta$  is a discrete random variable which assumes the value  $i \in \{1, \dots, K\}$  with probability  $(\lambda_i(z)/\lambda_0(z))$ .

Later we shall establish tau-convergence of our sensitivity estimator by showing that for a fixed tau-leap method  $\alpha$ , the bias incurred by our estimator converges to 0 as the coarseness  $|\beta|$  of the time-discretization scheme goes to 0. For this we shall require (weak) convergence of all moments of the tau-leap process to those of the exact process. We now state this requirement more precisely and present a simple lemma that will be needed later. For  $p \geq 0$ , we say that a function  $f : \mathbb{N}_0^d \rightarrow \mathbb{R}$  is of class  $\mathcal{C}_p$  if there exists a positive constant  $C$  such that

$$|f(x)| \leq C(1 + \|x\|^p) \quad \text{for all } x \in \mathbb{N}_0^d. \quad (2.19)$$

We shall require that a tau-leap method  $\alpha$  satisfies an order  $\gamma > 0$  convergent error bound. This is stated formally by Assumption 1 and it can be verified using the results in [35].

**Assumption 1** Given a tau-leap method  $\alpha$ , there exist  $\gamma > 0$ ,  $\delta > 0$  and a mapping  $\xi : \mathbb{R}_+ \rightarrow \mathbb{R}_+$  such that, for every  $p \geq 0$  and every final time  $T > 0$ , there exists a constant  $C_1(p, T, \alpha)$  satisfying

$$\begin{aligned} \sup_{t \in [0, T]} |\mathbb{E}(\|Z_{\alpha,\beta}(x_0, t)\|^p) - \mathbb{E}(\|X(x_0, t)\|^p)| &\leq \sup_{t \in [0, T]} \sum_{y \in \mathbb{N}_0^d} (1 + \|y\|^p) |\mathbb{P}(Z_{\alpha,\beta}(x_0, t) = y) - \mathbb{P}(X(x_0, t) = y)| \\ &\leq C_1(p, T, \alpha)(1 + \|x_0\|^{\xi(p)})|\beta|^\gamma, \end{aligned} \quad (2.20)$$

for any initial state  $x_0$  provided that  $|\beta| \leq \delta$ . Note that here the second inequality is our assumption while the first inequality always holds.

Additionally we will require Assumptions 2 and 3 on moment growth bounds of the exact process as well as the tau-leap process. These assumptions can be verified using the results in [34, 24, 35].

**Assumptions 2 and 3** Given a tau-leap method  $\alpha$ , there exists  $\delta > 0$  such that for each  $T > 0$  and  $p \geq 0$  there exist constants  $C_2(p, T)$  and  $C_3(p, T, \alpha)$  satisfying

$$\begin{aligned} \sup_{t \in [0, T]} (1 + \mathbb{E}(\|X(x_0, t)\|^p)) &\leq C_2(p, T)(1 + \|x_0\|^p) \\ \text{and} \quad \sup_{t \in [0, T]} (1 + \mathbb{E}(\|Z_{\alpha,\beta}(x_0, t)\|^p)) &\leq C_3(p, T, \alpha)(1 + \|x_0\|^p), \end{aligned} \quad (2.21)$$

for all  $t \in [0, T]$ , provided  $|\beta| \leq \delta$ .

We emphasize that constants  $C_1$  and  $C_3$  in Assumptions 1 and 3, do not depend on the step-size selection strategy  $\beta$ , and all the three constants in these assumptions may be assumed to be monotonic in  $T$  without any loss of generality. The following lemma follows readily from the above assumptions.

**Lemma 2.2** Consider a function  $\phi : \mathbb{N}_0^d \times [0, T] \rightarrow \mathbb{R}$  and suppose that there exists a constant  $C > 0$  such that  $\sup_{t \in [0, T]} |\phi(x, t)| \leq C(1 + \|x\|^p)$  for all  $x \in \mathbb{N}_0^d$ . Then under Assumptions 1, 2 and 3, we have

$$\begin{aligned} \sup_{t \in [0, T]} |\mathbb{E}(\phi(Z_{\alpha, \beta}(x_0, t), t)) - \mathbb{E}(\phi(X(x_0, t), t))| &\leq CC_1(p, T, \alpha)(1 + \|x_0\|^{\xi(p)})|\beta|^\gamma, \\ \sup_{t \in [0, T]} |\mathbb{E}(\phi(X(x_0, t), t))| &\leq CC_2(p, T)(1 + \|x_0\|^p) \\ \text{and} \quad \sup_{t \in [0, T]} |\mathbb{E}(\phi(Z_{\alpha, \beta}(x_0, t), t))| &\leq CC_3(p, T, \alpha)(1 + \|x_0\|^p), \end{aligned} \quad (2.22)$$

provided  $|\beta| \leq \delta$ .

### 3 Main Results

In this section we present our approach for accurately estimating parameter sensitivities of the form (1.1) with *only* approximate tau-leap simulations of the dynamics. This approach is based on an exact *integral representation* for parameter sensitivity given by Theorem 3.1. With this representation at hand, we construct a tau-leap estimator for parameter sensitivity and examine its convergence properties as the time-discretization mesh gets finer and finer (see Sections 3.1 and 3.2). Thereafter in Section 3.3 we present an algorithm that computes the tau-leap estimator for sensitivity estimation.

Let  $(X_\theta(t))_{t \geq 0}$  be the Markov process representing reaction dynamics with initial state  $x_0$  and let  $\Psi_\theta(x, f, t)$  be defined by (2.14). For convenience, for any reaction  $k = 1, \dots, K$ , we define the difference operator  $\Delta_{\zeta_k}$  by

$$\Delta_{\zeta_k} h(x) = h(x + \zeta_k) - h(x),$$

for any function  $h : \mathbb{N}_0^d \rightarrow \mathbb{R}$ . The following theorem expresses the sensitivity value  $S_\theta(f, T)$  as the expectation of a random variable which can be computed from the paths of the process  $(X_\theta(t))_{t \geq 0}$  in the time interval  $[0, T]$ . The proof of this theorem is provided in the Appendix.

**Theorem 3.1** Suppose  $(X_\theta(t))_{t \geq 0}$  is the Markov process with generator  $\mathbb{A}_\theta$  and initial state  $x_0$ . Then the sensitivity value  $S_\theta(f, T)$  is given by

$$S_\theta(f, T) = \frac{\partial}{\partial \theta} \Psi_\theta(x_0, f, T) = \sum_{k=1}^K \mathbb{E} \left( \int_0^T \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} \Delta_{\zeta_k} \Psi_\theta(X_\theta(t), f, T - t) dt \right).$$

**Remark 3.2** This formula has the following simple interpretation. Due to an infinitesimal perturbation of parameter  $\theta$ , the probability that the process  $(X_\theta(t))_{t \geq 0}$  has an “extra” jump at time  $t$  in the direction  $\zeta_k$  is proportional to

$$\frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta}.$$

Moreover the change in the expectation of  $f(X_\theta(T))$  at time  $T$  due to this “extra” jump at time  $t$  is just

$$\Delta_{\zeta_k} \Psi_\theta(X_\theta(t) + \zeta_k, f, T - t).$$

The above result shows that the overall sensitivity of the expectation of  $f(X_\theta(x, T))$  is just the product of these two terms, integrated over the whole time interval  $[0, T]$ .

The rest of this section is devoted to the development of a tau-leap estimator for parameter sensitivity using this formula. To simplify our notations, we suppress the dependence on parameter  $\theta$ , and hence denote  $\lambda_k(\cdot, \theta)$  by  $\lambda_k(\cdot)$ ,  $\partial \lambda_k / \partial \theta$  by  $\partial \lambda_k$ ,  $S_\theta(f, T)$  by  $S(f, T)$ ,  $\Psi_\theta(x, f, t)$  by  $\Psi(x, f, t)$  and the process  $(X_\theta(t))_{t \geq 0}$  by  $(X(t))_{t \geq 0}$ . Due to Theorem 3.1 the sensitivity value  $S(f, T)$  can be expressed as

$$S(f, T) = \sum_{k=1}^K \mathbb{E} \left( \int_0^T \partial \lambda_k(X(t)) \Delta_{\zeta_k} \Psi(X(t), f, T - t) dt \right). \quad (3.23)$$

### 3.1 Sensitivity approximation with tau-leap simulations

In order to construct a tau-leap estimator for parameter sensitivity using formula (3.23), we need to replace both  $\partial\lambda_k(X(t))$  and  $\Delta_{\zeta_k}\Psi(X(t), f, T-t)$  with approximations derived with tau-leap simulations. Recall from Section 2.4 that a generic tau-leap scheme can be described by a pair of abstract labels  $\alpha$  and  $\beta$ , specifying the method and the step-size selection strategy respectively. Assuming such a tau-leap scheme is chosen, let the corresponding tau-leap process  $(Z_{\alpha,\beta}(x, t))_{t \geq 0}$  (see (2.18)) be an approximation for the exact dynamics starting at state  $x$ .

Suppose that we use the tau-leap method  $\alpha_0$  with the step-size selection strategy  $\beta_0$  to approximate  $X(t)$  and possibly a different tau-leap method  $\alpha_1$  with a time-dependent step-size selection strategy  $\beta_1(t)$  to compute an approximation of  $\Delta_{\zeta_k}\Psi(X(t), f, T-t)$ . This time-dependence in step-size selection is needed because the latter quantity requires simulation of *auxiliary* tau-leap paths in the interval  $[0, T-t]$  which varies with  $t$ . We discuss this in greater detail in the next section. In the following discussion, we will assume that both the tau-leap schemes  $(\alpha_0, \beta_0)$  and  $(\alpha_1, \beta_1(t))$  satisfy Assumptions 1, 2 and 3, with common  $\gamma > 0, \delta > 0$  and with  $|\beta|$  replaced by the supremum step-size

$$\tau_{\max} = \sup_{t \in [0, T]} \{|\beta_0|, |\beta_1(t)|\} \quad (3.24)$$

which is less than  $\delta$ . We define the tau-leap approximation of  $\Psi(x, f, t)$  (see (2.14)) by

$$\tilde{\Psi}_{\alpha,\beta}(x, f, t) = \mathbb{E}(f(Z_{\alpha,\beta}(x, t))), \quad (3.25)$$

and make the assumption that the step size selection strategy  $\beta_1(t)$  depends on  $t$  in such a way that  $t \mapsto \tilde{\Psi}_{\alpha_1, \beta_1(t)}(x, f, T-t)$  is a measurable function of  $t$ . Motivated by formula (3.23), we shall approximate the true sensitivity value  $S(f, t)$  by

$$\tilde{S}(f, T) = \sum_{k=1}^K \mathbb{E} \left( \int_0^T \partial\lambda_k(Z_{\alpha_0, \beta_0}(x_0, t)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t)}(Z_{\alpha_0, \beta_0}(x_0, t), f, T-t) dt \right), \quad (3.26)$$

where  $x_0$  is the starting state of the process  $(X(t))_{t \geq 0}$ . The next theorem, proved in the Appendix, shows that the bias of this sensitivity approximation is similar to the bias of the underlying tau-leap scheme. In particular if the tau-leap method satisfies order  $\gamma$  convergent error bound, then the same is true for the error incurred by the sensitivity approximation. Before we state the theorem, recall that for any  $p \geq 0$ , a function  $f : \mathbb{N}_0^d \rightarrow \mathbb{R}$  is in class  $\mathcal{C}_p$  if it satisfies (2.19) for some constant  $C \geq 0$ .

**Theorem 3.3** *Let  $f : \mathbb{N}_0^d \rightarrow \mathbb{R}$  as well as  $\partial\lambda_k$  for each  $k = 1, \dots, K$  be of class  $\mathcal{C}_p$  for some  $p \geq 0$ . Suppose that a tau-leap approximation  $\tilde{S}(f, T)$  of the exact sensitivity  $S(f, T)$  is computed by (3.26), where a tau-leap method  $\alpha_0$  with step size strategy  $\beta_0$  is used to approximate the underlying process  $(X(t))_{t \geq 0}$  and possibly a different tau-leap method  $\alpha_1$  with time-dependent step size strategy  $\beta_1(t)$  is used to compute approximations  $\tilde{\Psi}_{\alpha_1, \beta_1(t)}(x, f, T-t)$  of  $\Psi(x, f, T-t)$  at each  $t \in [0, T]$ . If both the tau-leap methods satisfy Assumptions 1, 2 and 3, with common  $\gamma > 0$  and  $\delta > 0$ , then there exists a constant  $\tilde{C}(f, T)$  such that*

$$|\tilde{S}(f, T) - S(f, T)| \leq \tilde{C}(f, T) \tau_{\max}^\gamma,$$

where  $\tau_{\max}$  is given by (3.24) and it is less than  $\delta$ .

**Remark 3.4** *In particular, this result shows that an unbiased estimator for  $\tilde{S}(f, T)$  will be a tau-convergent estimator for the true sensitivity value  $S(f, T)$  because the bias of such an estimator will converge to 0 as the supremum step-size  $\tau_{\max}$  converges to 0.*

### 3.2 A tau-leap estimator for parameter sensitivity

We now come to the problem of estimating the sensitivity approximation  $\tilde{S}(f, T)$  using tau-leap simulations. Expression (3.26) shows that  $\tilde{S}(f, T)$  is the expectation of the random variable  $\bar{s}(f, T)$  defined by

$$\bar{s}(f, T) = \sum_{k=1}^K \int_0^T \partial\lambda_k(Z_{\alpha_0, \beta_0}(x_0, t)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t)}(Z_{\alpha_0, \beta_0}(x_0, t), f, T-t) dt. \quad (3.27)$$

If we can generate samples of this random variable, then the estimation of  $\tilde{S}(f, T)$  would be quite straightforward using (2.6). However this is not the case as the random variable  $\bar{s}(f, T)$  is nearly impossible to generate. This is mainly because it requires computing quantities of the form

$$\Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t)}(Z_{\alpha_0, \beta_0}(x_0, t), f, T - t) \quad (3.28)$$

at infinitely many time points  $t$ . These quantities generally do not have an explicit formula and hence they need to be estimated via auxiliary Monte Carlo simulations, which severely restricts the number of such quantities that can be feasibly estimated. We tackle these problems by constructing another random variable  $\tilde{s}(f, T)$  whose expected value equals  $\tilde{S}(f, T)$ , and whose samples can be easily generated using a simple procedure called  $\tau$ BPA (Tau Bernoulli Path Algorithm) that is described in Section 3.3. This random variable is constructed by *adding randomness* to the random variable  $\bar{s}(f, T)$  in such a way that only a small finite number of unknown quantities of the form (3.28) require estimation. We now present this construction.

Recall from Section 2.4 the description of the tau-leap process  $(Z_{\alpha_0, \beta_0}(x_0, t))_{t \geq 0}$  which approximates the exact dynamics  $(X(t))_{t \geq 0}$ . Let  $0 = t_0 < t_1 < \dots < t_\mu = T$  be the (possibly random) mesh corresponding to step size selection strategy  $\beta_0$ . Let  $\tau_i = t_{i+1} - t_i$  and define

$$\sigma_i = t_i + u_i \tau_i, \quad (3.29)$$

where each  $u_i$  is an independent random variable with distribution Uniform $[0, 1]$ . Thus given  $t_i$  and  $t_{i+1}$ , the distribution of  $\sigma_i$  is Uniform $[t_i, t_{i+1}]$ . Moreover taking expectation over the distribution of  $u_i$  we get

$$\begin{aligned} & \tau_i \mathbb{E} \left( \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(\sigma_i)}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i), f, T - \sigma_i) \middle| \mathcal{F}_T \right) \\ &= \tau_i \int_0^1 \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, t_i + u \tau_i)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t_i + u \tau_i)}(Z_{\alpha_0, \beta_0}(x_0, t_i + u \tau_i), f, T - t_i - u \tau_i) du \\ &= \int_{t_i}^{t_{i+1}} \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, t)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t)}(Z_{\alpha_0, \beta_0}(x_0, t), f, T - t) dt, \end{aligned} \quad (3.30)$$

where  $\mathcal{F}_T$  denotes the  $\sigma$ -algebra generated by the process  $(Z_{\alpha_0, \beta_0}(x_0, t))_{t \geq 0}$  and the random mesh  $\beta_0$  over the interval  $[0, T]$ , and the last equality follows from the substitution  $t = t_i + u \tau_i$ . Using this relation along with (3.26) we get

$$\begin{aligned} \tilde{S}(f, T) &= \sum_{k=1}^K \mathbb{E} \left( \int_0^T \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, t)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t)}(Z_{\alpha_0, \beta_0}(x_0, t), f, T - t) dt \right) \\ &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0}^{\mu-1} \int_{t_i}^{t_{i+1}} \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, t)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(t)}(Z_{\alpha_0, \beta_0}(x_0, t), f, T - t) dt \right) \\ &= \sum_{k=1}^K \mathbb{E} \left[ \sum_{i=0}^{\mu-1} \tau_i \mathbb{E} \left( \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(\sigma_i)}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i), f, T - \sigma_i) \middle| \mathcal{F}_T \right) \right] \\ &= \sum_{k=1}^K \mathbb{E} \left[ \mathbb{E} \left( \sum_{i=0}^{\mu-1} \tau_i \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(\sigma_i)}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i), f, T - \sigma_i) \middle| \mathcal{F}_T \right) \right] \\ &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0}^{\mu-1} \tau_i \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i)) \Delta_{\zeta_k} \tilde{\Psi}_{\alpha_1, \beta_1(\sigma_i)}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i), f, T - \sigma_i) \right). \end{aligned} \quad (3.31)$$

In deriving this relation we have used the fact that both  $\tau_i$  and  $\mu$  are measurable with respect to the sigma algebra  $\mathcal{F}_T$  and the expectation operator is linear.

To proceed further we define a “conditional estimator”  $\hat{D}_{ki}$  of the quantity (3.28) at  $t = \sigma_i$  by

$$\hat{D}_{ki} = f(Z_{\alpha_1, \beta_1(\sigma_i)}^{1ki}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i) + \zeta_k, T - \sigma_i)) - f(Z_{\alpha_1, \beta_1(\sigma_i)}^{2ki}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i), T - \sigma_i)) \quad (3.32)$$

where  $Z^{1ki}$  and  $Z^{2ki}$  are instances of tau-leap approximations of the exact dynamics starting at initial states  $(Z_{\alpha_0, \beta_0}(x_0, \sigma_i) + \zeta_k)$  and  $Z_{\alpha_0, \beta_0}(x_0, \sigma_i)$  respectively. Both these tau-leap processes use the same method

$\alpha_1$  and the same step-size selection strategy  $\beta_1(\sigma_i)$ . Moreover conditioned on  $Z_{\alpha_0, \beta_0}(x_0, \sigma_i)$  and  $\sigma_i$ , the processes  $Z^{1ki}, Z^{2ki}$  and the step-size selection strategy  $\beta_1(\sigma_i)$  are independent of the process  $Z_{\alpha_0, \beta_0}$  and the step-size selection strategy  $\beta_0$ . Therefore it is immediate that

$$\mathbb{E}(\widehat{D}_{ki} | Z_{\alpha_0, \beta_0}(x_0, \sigma_i), \sigma_i) = \Delta_{\zeta_k} \widetilde{\Psi}_{\alpha_1, \beta_1(\sigma_i)}(Z_{\alpha_0, \beta_0}(x_0, \sigma_i), f, T - \sigma_i), \quad (3.33)$$

and hence from (3.31) we obtain the following representation for  $\widetilde{S}(f, T)$

$$\widetilde{S}(f, T) = \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0}^{\mu-1} \tau_i \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i)) \widehat{D}_{ki} \right). \quad (3.34)$$

An estimator for  $\widetilde{S}(f, T)$  based on this formula can require several computations of  $\widehat{D}_{ki}$  because the number of leaps ( $\mu$ ) in the time interval  $[0, T]$  can be very large. Since each evaluation of  $\widehat{D}_{ki}$  is computationally expensive, we would like to achieve a reduction in the number of these evaluations by randomizing the decision of whether  $\widehat{D}_{ki}$  should be evaluated at time  $\sigma_i$  or not. Moreover this randomization must be performed without introducing a bias in the estimator. We now describe this process.

For each  $i = 0, 1, \dots, (\mu - 1)$  and  $k = 1, \dots, K$  let  $R_{ki}$  and  $\beta_{ki}$  be given by

$$R_{ki} = |\partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i))| \tau_i \quad \text{and} \quad \beta_{ki} = \text{Sign}(\partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i))).$$

Fix a normalizing constant  $C > 0$ . The choice of  $C$  and its role will be explained later in the section. If  $R_{ki} > 0$  then let  $\rho_{ki}$  be an independent  $\{0, 1\}$ -valued random variable whose distribution is Bernoulli with

$$P_{ki} = \mathbb{P}(\rho_{ki} = 1 | Z_{\alpha_0, \beta_0}(x_0, \sigma_i), \tau_i) = \left( \frac{R_{ki}}{C} \right) \wedge 1. \quad (3.35)$$

Define  $L_{ki}$  by

$$L_{ki} = \begin{cases} 0 & \text{if } R_{ki} = 0 \\ \frac{R_{ki}}{P_{ki}} & \text{otherwise} \end{cases}$$

and note that

$$\mathbb{E}(\beta_{ki} \rho_{ki} L_{ki} | Z_{\alpha_0, \beta_0}(x_0, \sigma_i), \tau_i) = R_{ki} \beta_{ki} = \partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, \sigma_i)) \quad (3.36)$$

which also shows that

$$\widetilde{S}(f, T) = \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0}^{\mu-1} \beta_{ki} \rho_{ki} L_{ki} \widehat{D}_{ki} \right). \quad (3.37)$$

This formula suggests that  $\widetilde{S}(f, T)$  can be estimated, without any bias, using realizations of the random variable

$$\widetilde{s}(f, T) = \sum_{k=1}^K \sum_{i=0}^{\mu-1} \beta_{ki} \rho_{ki} L_{ki} \widehat{D}_{ki}. \quad (3.38)$$

In generating each realization of  $\widetilde{s}(f, T)$ , the computation of  $\widehat{D}_{ki}$  is only needed if the Bernoulli random variable  $\rho_{ki}$  is 1. Therefore, if we can effectively control the number of such  $\rho_{ki}$ -s then we can efficiently generate realizations of  $\widetilde{s}(f, T)$ . This can be achieved using the positive parameter  $C$  (see (3.35)) as we soon explain. Based on the construction outlined above, we provide a method in Section 3.3 for obtaining realizations of the random variable  $\widetilde{s}(f, T)$ . We call this method, the *Tau Bernoulli Path Algorithm* ( $\tau$ BPA), because at each  $\sigma_i$ , the decision of whether  $\widehat{D}_{ki}$  must be computed or not is based on the value of a Bernoulli random variable  $\rho_{ki}$ . Using  $\tau$ BPA we can efficiently generate realizations  $s_1, s_2, \dots$  of  $\widetilde{s}(f, T)$  and approximately estimate the parameter sensitivity  $\widetilde{S}(f, T)$  with the estimator (2.6).

We mentioned before that  $\widetilde{s}(f, T)$  is obtained by adding extra randomness to the random variable  $\widetilde{s}(f, T)$  given by (3.27). This addition of randomness must be minimized to improve the efficiency of the estimator.

Since  $\mathbb{E}(\tilde{s}(f, T) | \mathcal{F}_T) = \bar{s}(f, T)$ , this increase in variance is equal to  $\text{Var}(\tilde{s}(f, T) | \mathcal{F}_T)$ , and in order to reduce this quantity we focus on reducing the conditional variance  $\text{Var}(\hat{D}_{ki} | \mathcal{F}_T)$ . Recall that  $\hat{D}_{ki}$  is given by (3.32) and for convenience we abbreviate  $Z_{\alpha_1, \beta_1(\sigma_i)}^{lki}$  by  $Z^l$  for  $l = 1, 2$ . The reduction in this conditional variance can be accomplished by tightly coupling the pair of processes  $(Z^1, Z^2)$ . For this purpose we use the split-coupling (recall (2.12)-(2.13)) specified by

$$Z^1(t) = (Z_{\alpha_0, \beta_0}(x_0, \sigma_i) + \zeta_k) + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(Z^1(\eta(s)), \theta) \wedge \lambda_k(Z^2(\eta(s)), \theta) ds \right) \zeta_k \quad (3.39)$$

$$+ \sum_{k=1}^K Y_k^{(1)} \left( \int_0^t (\lambda_k(Z^1(\eta(s)), \theta) - \lambda_k(Z^1(\eta(s)), \theta) \wedge \lambda_k(Z^2(\eta(s)), \theta)) ds \right) \zeta_k$$

and

$$Z^2(t) = Z_{\alpha_0, \beta_0}(x_0, \sigma_i) + \sum_{k=1}^K Y_k \left( \int_0^t \lambda_k(Z^1(\eta(s)), \theta) \wedge \lambda_k(Z^2(\eta(s)), \theta) ds \right) \zeta_k \quad (3.40)$$

$$+ \sum_{k=1}^K Y_k^{(2)} \left( \int_0^t (\lambda_k(Z^2(\eta(s)), \theta) - \lambda_k(Z^1(\eta(s)), \theta) \wedge \lambda_k(Z^2(\eta(s)), \theta)) ds \right) \zeta_k,$$

where  $\{Y_k, Y_k^{(1)}, Y_k^{(2)} : k = 1, \dots, K\}$  is an independent family of unit rate Poisson processes. Here  $\eta(s) = t_i$  for  $t_i \leq s < t_{i+1}$ , and  $\{t_0, t_1, t_2, \dots\}$  is the sequence of leap-times of the pair of processes  $(Z^1, Z^2)$  jointly simulated with the tau-leap scheme  $(\alpha_1, \beta_1(t))$ .

We now discuss how the positive parameter  $C$  can be selected. Let  $\eta_{\text{req}}$  be the random variable denoting the total number of  $\rho_{ki}$ -s that assume the value 1 in (3.38). This is the number of  $\hat{D}_{ki}$ -s that are required to obtain a realization of  $\tilde{s}(f, T)$ . It is immediate that  $\eta_{\text{req}}$  is bounded above by  $\rho_{\text{tot}} = \sum_{k=1}^K \sum_{i=1}^{\mu-1} \rho_{ki}$ . Given the sigma field  $\mathcal{F}_T$ ,  $\rho_{\text{tot}}$  is a  $\mathbb{N}_0$ -valued random variable whose expectation is given by:

$$\mathbb{E}(\rho_{\text{tot}} | \mathcal{F}_T) = \sum_{k=1}^K \sum_{i=1}^{\mu-1} P_{ki} = \sum_{k=1}^K \sum_{i=1}^{\mu-1} \left( \frac{R_{ki}}{C} \right) \wedge 1.$$

Since  $a \wedge b \leq a$  we obtain

$$\begin{aligned} \mathbb{E}(\rho_{\text{tot}}) &= \mathbb{E}(\mathbb{E}(\rho_{\text{tot}} | \mathcal{F}_T)) = \mathbb{E} \left( \sum_{k=1}^K \sum_{i=1}^{\mu-1} \left( \frac{R_{ki}}{C} \right) \wedge 1 \right) \leq \frac{1}{C} \sum_{k=1}^K \mathbb{E} \left( \sum_{i=1}^{\mu-1} R_{ki} \right) \\ &= \frac{1}{C} \sum_{k=1}^K \mathbb{E} \left( \int_0^T |\partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, t))| dt \right). \end{aligned}$$

We choose a small positive integer  $M_0$  and set

$$C = \frac{1}{M_0} \sum_{k=1}^K \mathbb{E} \left( \int_0^T |\partial \lambda_k(Z_{\alpha_0, \beta_0}(x_0, t))| dt \right), \quad (3.41)$$

where the expectation can be approximately estimated using  $N_0$  tau-leap simulations of the dynamics in the time interval  $[0, T]$ . Such a choice ensures that  $\rho_{\text{tot}}$  is bounded above by  $M_0$  on average. Note that  $\tau$ BPA will provide an unbiased estimator for  $\tilde{S}(f, T)$  regardless of the choice of  $M_0$ . The parameter  $M_0$  plays the same role as in PPA (see Section 2.2), namely, it allows one to select the trade-off between the computational cost  $\mathcal{C}(\tau\text{BPA})$  and the variance  $\mathcal{V}(\tau\text{BPA})$ . A higher value of  $M_0$  reduces the variance but it also increases the computational cost. In the examples we consider in Section 4 we fix  $M_0$  to be 10. However it is conceivable that there exist strategies for optimally selecting  $M_0$  based on the network of interest and the observation time period. We leave this issue for future research.

### 3.3 The Tau Bernoulli Path Algorithm ( $\tau$ BPA)

We now provide a detailed description of the method  $\tau$ BPA which produces realizations of the random variable  $\tilde{s}(f, T)$  defined by (3.38). Computing the empirical mean (2.6) of these realizations estimates the



approximate parameter sensitivity  $\tilde{S}(f, T)$ . Throughout this section we assume that the function  $rand()$  returns independent samples from the distribution  $\text{Uniform}[0, 1]$ .

The method  $\tau\text{BPA}$  can be adapted to work with any tau-leap scheme, but for concreteness, we assume that an *explicit* tau-leap scheme is used for all the simulations. This means that the current state  $z$  and time  $t$ , are sufficient to determine the distributions of the next time-step  $\tau$  and the vector of reaction firings  $\tilde{R} = (\tilde{R}_1, \dots, \tilde{R}_K)$  in the time interval  $[t, t + \tau)$ . We suppose that a sample from these two distributions can be obtained using the methods  $\text{GETTAU}(z, t, T)$ <sup>2</sup> and  $\text{GETREACTIONFIRINGS}(z, \tau)$  respectively. If we use the simplest tau-leap scheme given in [19], then reaction firings can be generated as

$$\tilde{R}_k = \text{POISSON}(\lambda_k(z)\tau), \quad (3.42)$$

for  $k = 1, \dots, K$ , where the function  $\text{POISSON}(r)$  generates an independent Poisson random variable with mean  $r$ .

Let  $Z$  denote the tau-leap process approximating the reaction dynamics with initial state  $x_0$ . Our first task is to select a normalization parameter  $C$  according to (3.41), by estimating the expectation in the formula using  $N_0$  simulations of the process  $Z$ . This is done using the function  $\text{SELECT-NORMALIZING-CONSTANT}(x_0, M_0, T)$  (see Algorithm 2) where  $M_0$  is a small number that upper-bounds the expected number of unknown quantities ( $\hat{D}_{ki}$ -s) that need to be estimated (see Section 3.2). Once  $C$  is chosen, a single realization of  $\tilde{s}_\theta(f, T)$  can be computed using  $\text{GENERATESAMPLE}(x_0, T, C)$  (Algorithm 1). This method simulates the tau-leap process  $Z$  and at each leap-time  $t_i$ , the following happens:

- The next leap size  $\tau_i (= \tau)$  and the random variable  $\sigma_i (= \sigma)$  are computed.
- The state is updated to get the state-value  $z = Z(\sigma_i)$  at time  $\sigma_i$ .
- For each reaction  $k$ , the variables  $\beta_{ki} (= \beta)$ ,  $R_{ki} (= R)$ ,  $P_{ki} (= P)$  and  $\rho_{ki} (= \rho)$  are generated. The function  $\text{BERNOULLI}(P)$  generates an independent Bernoulli random variable with expectation  $P$ .
- If  $\rho_{ki} = 1$  then  $\hat{D}_{ki}$  (see (3.32)) is evaluated using  $\text{EVALUATECOUPLEDDIFFERENCE}(z, z + \zeta_k, \sigma, T)$  (see Algorithm 3) and the sample value is updated according to (3.38). This method independently simulates the pair of processes  $(Z^1, Z^2)$  specified by the split-coupling (3.39)-(3.40) in order to compute  $\hat{D}_{ki}$ . For simplicity we assume that these simulations are carried out by the tau-leap scheme which generates reaction firings according to (3.42).

Observe that generating a single realization of  $\tilde{s}(f, T)$  using Algorithm 1 requires twice as many “leaps” as simulating the tau-leap process  $Z$  in the interval  $[0, T]$ . This is because between any two successive leaps  $t_i$  and  $t_{i+1}$ , an extra leap (at  $\sigma_i$ ) is placed uniformly in the interval  $[t_i, t_{i+1}]$ , for generating a realization of  $\tilde{s}(f, T)$ .

## 4 Numerical Examples

In this section we computationally compare six sensitivity estimation methods on many examples. The methods we consider are the following:

1. **Tau Bernoulli Path Algorithm** or  $\tau\text{BPA}$ : This is the method described in Section 3.3. The tau-leap scheme we use is the simple Euler method [19] with Poisson reaction firings (3.42) and uniform step-size  $\tau = 0.1T$ , where  $T$  is the final time at which the sensitivity is to be estimated. With this step-size it is possible to *leap over* the final time  $T$  in the computation of  $\hat{D}_{ki}$ -s by Algorithm 3. To guard against this possibility we set

$$\text{GETTAU}(z, t, T) = \min\{0.1T, T - t\}.$$

Moreover the parameter  $M_0$  in  $\tau\text{BPA}$  is fixed at 10.

---

<sup>2</sup>We allow the step-size selection to depend on both the current time  $t$  and the final time  $T$ . This is especially important for simulating the auxiliary paths that are required to compute the  $\hat{D}_{ki}$ -s in (3.38) (see Sections 3.1 and 3.2).

---

**Algorithm 1** Generates one realization of  $\tilde{s}(f, T)$  according to (3.38)

---

```

1: function GENERATESAMPLE( $x_0, T, C$ )
2:   Set  $z = x_0, t = 0$  and  $s = 0$ 
3:   while  $t < T$  do
4:     Calculate  $\tau = \text{GETTAU}(z, t, T)$ 
5:      $\sigma \leftarrow (t + \text{rand}()) \times \tau$ 
6:     Set  $(\tilde{R}_1, \dots, \tilde{R}_K) = \text{GETREACTIONFIRINGS}(z, \sigma - t)$ .
7:     Set  $z \leftarrow z + \sum_{k=1}^K \zeta_k \tilde{R}_k$ .
8:     for  $k = 1$  to  $K$  do
9:       Set  $R = |\partial \lambda_k(z)| \tau$  and  $\beta = \text{Sign}(\partial \lambda_k(z))$ 
10:      Set  $P = \min\{R/C, 1\}$  and  $\rho = \text{BERNOULLI}(P)$ 
11:      if  $\rho = 1$  then
12:        Update  $s \leftarrow s + \left(\frac{\beta R}{P}\right) \text{EVALUATECOUPLEDDIFFERENCE}(z, z + \zeta_k, \sigma, T)$ 
13:      end if
14:    end for
15:    Update  $t \leftarrow t + \tau$ 
16:    Set  $(\tilde{R}_1, \dots, \tilde{R}_K) = \text{GETREACTIONFIRINGS}(z, t - \sigma)$ .
17:    Set  $z \leftarrow z + \sum_{k=1}^K \zeta_k \tilde{R}_k$ .
18:  end while
19:  return  $s$ 
20: end function

```

---

2. **Exact Bernoulli Path Algorithm** or **eBPA**: This is the method we obtain by replacing the tau-leap simulations in  $\tau$ BPA with the exact simulations performed with Gillespie's SSA [18]. This replacement can be easily made by choosing the step-size and the reaction firings according to Remark 2.1. Moreover we need to change the method  $\text{EVALUATECOUPLEDDIFFERENCE}(z_1, z_2, t, T)$  to the version given in [26]. Note that eBPA is a new unbiased method for estimating parameter sensitivity, like the methods in Section 2.2. This method is conceptually similar to PPA [26], which is based on the formula (2.16). However unlike this formula, the formula (3.23) underlying  $\tau$ BPA does not involve summation over the jumps of the process, which makes it more amenable for incorporating tau-leap schemes.
3. **Exact Coupled Finite Difference** or **eCFD**: This is same as the CFD method in [2]. It is based on the coupling (2.12)-(2.13).
4. **Exact Common Reaction Paths** or **eCRP**: This is same as the CRP method in [40]. It is based on the coupling (2.10)-(2.11).
5. **Tau Coupled Finite Difference** or  $\tau$ **CFD**: We propose this method as the tau-leap version of CFD. The coupling (2.12)-(2.13) is approximated by setting the reaction firings as we now describe. Let  $(Z_\theta, Z_{\theta+h})$  be the pair of tau-leap processes that approximate the processes  $(X_\theta, X_{\theta+h})$ , and suppose that at leap time  $t_i$  their state is  $(Z_\theta(t_i), Z_{\theta+h}(t_i)) = (z_1, z_2)$ . If the next step-size is  $\tau$ , then we set the number of firings  $(\tilde{R}_{\theta,k}, \tilde{R}_{\theta+h,k})$  for this pair of processes as

$$A_k = \text{POISSON}((\lambda_k(z_1) \wedge \lambda_k(z_2))\tau), \quad \tilde{R}_{\theta,k} = A_k + \text{POISSON}((\lambda_k(z_1) - \lambda_k(z_1) \wedge \lambda_k(z_2))\tau)$$

and  $\tilde{R}_{\theta+h,k} = A_k + \text{POISSON}((\lambda_k(z_2) - \lambda_k(z_1) \wedge \lambda_k(z_2))\tau)$

for every reaction  $k = 1, \dots, K$ . Such a selection of reaction firings emulates the coupling (2.12)-(2.13).

6. **Tau Common Reaction Paths** or  $\tau$ **CRP**: We propose this method as the tau-leap version of CRP where the coupling (2.10)-(2.11) is again devised by coupling the Poisson random variables that generate the reaction firings. Using the same notation as before, if  $(Z_\theta(t_i), Z_{\theta+h}(t_i)) = (z_1, z_2)$  and the next step-size is  $\tau$ , then to approximately realize the coupling (2.10)-(2.11) we set the number of firings  $(\tilde{R}_{\theta,k}, \tilde{R}_{\theta+h,k})$  as

$$\tilde{R}_{\theta,k} = \text{POISSON}(\lambda_k(z_1)\tau, k) \quad \text{and} \quad \tilde{R}_{\theta+h,k} = \text{POISSON}(\lambda_k(z_2)\tau, k)$$

---

**Algorithm 2** Estimates the normalizing constant  $C$  using  $N_0$  simulations of the tau-leap process  $Z$

---

```

1: function SELECT-NORMALIZING-CONSTANT( $x_0, M_0, T$ )
2:   Set  $S = 0$ 
3:   for  $i = 1$  to  $N_0$  do
4:     Set  $z = x_0$  and  $t = 0$ 
5:     while  $t < T$  do
6:       Calculate  $\tau = \text{GETTAU}(z, t, T)$ 
7:       for  $k = 1$  to  $K$  do
8:         Update  $S \leftarrow S + \tau |\partial \lambda_k(z)|$ 
9:       end for
10:      Update  $t \leftarrow t + \tau$ 
11:      Set  $(\tilde{R}_1, \dots, \tilde{R}_K) = \text{GETREACTIONFIRINGS}(z, \tau)$ .
12:      Set  $z \leftarrow z + \sum_{k=1}^K \zeta_k \tilde{R}_k$ .
13:    end while
14:  end for
15:  return  $S/(N_0 M_0)$ 
16: end function

```

---

**Algorithm 3** Used to evaluate  $\hat{D}_{ki}$  given by (3.32)

---

```

1: function EVALUATECOUPLEDDIFFERENCE( $z_1, z_2, t, T$ )
2:   while  $z_1 \neq z_2$  AND  $t < T$  do
3:     Set  $\tau_1 = \text{GETTAU}(z_1, t, T)$ ,  $\tau_2 = \text{GETTAU}(z_2, t, T)$  and  $\tau = \tau_1 \wedge \tau_2$ 
4:     for  $k = 1$  to  $K$  do
5:       Set  $A_{k1} = \lambda_k(z_1) \wedge \lambda_k(z_2)$ ,  $A_{k2} = \lambda_k(z_1) - A_{k1}$  and  $A_{k3} = \lambda_k(z_2) - A_{k1}$ 
6:       Set  $\tilde{R}_{ki} = \text{POISSON}(A_{ki}\tau)$  for  $i = 1, 2, 3$ 
7:       Update  $z_1 \leftarrow z_1 + \tilde{R}_{k1}\zeta_k + \tilde{R}_{k2}\zeta_k$ 
8:       Update  $z_2 \leftarrow z_2 + \tilde{R}_{k1}\zeta_k + \tilde{R}_{k3}\zeta_k$ 
9:       Update  $t \leftarrow t + \tau$ 
10:    end for
11:  end while
12:  return  $f(z_2) - f(z_1)$ 
13: end function

```

---

for every reaction  $k = 1, \dots, K$ . Here we assume that there are  $K$  parallel streams of independent Uniform[0, 1] random variables (see [40]), and the method POISSON( $r, k$ ) uses the uniform random variable from the  $k$ -th stream for generating the Poisson random variable with mean  $r$ .

In all the finite-difference schemes, we use perturbation-size  $h = 0.1$  and we *center* the parameter perturbations to obtain better accuracy. This centering can be easily achieved by substituting  $\theta$  with  $(\theta - h/2)$  and  $(\theta + h)$  with  $(\theta + h/2)$  in the expression (2.9) and also in the definition of the coupled processes. Since we use Poisson random variables to generate the reaction firings for tau-leap simulations, it is possible that some state-components become negative during the simulation run. In this paper we deal with this problem rather crudely by setting the negative state-components to 0. We have checked that this does not cause a significant loss of accuracy because the state-components become negative *very rarely*.

Note that among the methods considered here, eBPA is the only unbiased sensitivity estimation method. All the other methods are biased either due to a finite-difference approximation of the derivative (eCFD and eCRP) or due to tau-leap approximation of the sample paths ( $\tau$ BPA) or due to both these reasons ( $\tau$ CFD and  $\tau$ CRP). For each method we judge its accuracy using the following metric: if the exact sensitivity value is  $s_0$  and the estimated value is  $s$ , then the relative error (in percentage) for the methods is given by

$$\text{Relative Error} = \left| \frac{s - s_0}{s_0} \right| \times 100. \quad (4.43)$$

In the examples, we apply each sensitivity estimation method with a sample-size of  $N = 10^5$ , and compute

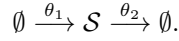
the estimator mean  $\hat{\mu}_N$  (2.6), the standard deviation  $\hat{\sigma}_N$  (2.8), the relative error (4.43) and the computational time. We then use quantities to compare the different estimation methods.

As we can expect, the exact schemes (eBPA, eCFD and eCRP) take much longer to run than their tau-leap counterparts ( $\tau$ BPA,  $\tau$ CFD and  $\tau$ CRP). In comparison to eCFD or eCRP, eBPA is always *slower* because it needs to additionally generate around 10 coupled-auxiliary paths. However eBPA is usually more *accurate* than both eCFD and eCRP, because of its unbiasedness. This advantage in accuracy over finite-difference schemes is greatly enhanced when we compare  $\tau$ BPA with  $\tau$ CFD and  $\tau$ CRP. This is possibly because the two sources of bias (finite-difference and tau-leap approximations) in  $\tau$ CFD and  $\tau$ CRP generally pile on top of each other, instead of counteracting each other. On comparing the standard deviations we find that these remain relatively unchanged when we switch from an exact scheme to its tau-leap version. This suggests that tau-leap simulations largely neglect the unimportant sources of variations in the dynamics and it supports our claim in Section 2.3, that substituting exact paths with tau-leap trajectories allows one to trade-off bias with computational costs, without affecting the variance significantly. In other words, tau-leap schemes provide a trade-off relationship that is “orthogonal” to other trade-off relationships shown in Table 1.

In all the examples below, the propensity functions  $\lambda_k$ -s for all the reactions have the mass-action form [3] unless stated otherwise. Also  $\partial$  always denotes the partial-derivative w.r.t. the designated sensitive parameter  $\theta$ .

## 4.1 Single-species birth-death model

Our first example is a simple birth-death model in which a single species  $\mathcal{S}$  is created and destroyed according to the following two reactions:



Let  $\theta_1 = 100$ ,  $\theta_2 = 1$  and assume that the sensitive parameter is  $\theta = \theta_2$ . Let  $(X(t))_{t \geq 0}$  be the Markov process representing the reaction dynamics. Assume that  $X(0) = 0$ . For  $f(x) = x$  we wish to estimate

$$S_\theta(f, T) = \partial \mathbb{E}(f(X(T))) = \partial \mathbb{E}(X(T))$$

for  $T = 0.3$  and  $T = 1$ . For each  $T$  we estimate the sensitivity using all the six methods and the estimator mean and standard deviation are displayed in Table 2. For this network we can compute the sensitivity  $S_\theta(f, T)$  exactly as the propensity functions are affine. These exact values are stated in the *caption* of Table 2, and they allow us to compute the *relative error* of an estimate according to (4.43). We compare these relative errors and the CPU times<sup>3</sup> for all the methods in Figure 1.

	eBPA		eCFD		eCRP	
$T$	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
0.3	-3.6907	0.0037	-3.6997	0.0176	-3.6877	0.0193
1	-26.4227	0.0308	-26.4679	0.0377	-26.3835	0.0517
	$\tau$ BPA		$\tau$ CFD		$\tau$ CRP	
$T$	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
0.3	-3.7208	0.0029	-3.4466	0.0173	-3.4633	0.0168
1	-26.6468	0.0215	-26.3828	0.0395	-26.3667	0.0316

Table 2: **Birth-death model:** Sensitivity estimation results for  $T = 0.3, 1$ . For all the methods, the estimator mean (2.6) and standard deviation (2.8) are obtained for  $N = 10^5$ . The exact sensitivity values are  $-3.6936$  for  $T = 0.3$  and  $-26.4241$  for  $T = 1$ .

From these numerical results we can make the following observations:

<sup>3</sup>All the computations in this paper were performed using C++ programs on an Apple machine with the 2.9 GHz Intel Core i5 processor.

- The exact methods are typically more accurate than the tau-leap methods but they require more CPU time.
- For  $T = 0.3$ , eCFD/eCRP are far more accurate than  $\tau$ CFD/ $\tau$ CRP suggesting that the two sources of bias (finite-difference and tau-leap approximations) are additive in nature. However the same is not true for  $T = 1$ .
- For  $T = 0.3$ ,  $\tau$ BPA is 5.5 times *slower* than  $\tau$ CFD but it is 9 times more accurate. This accuracy factor is maintained for  $\tau$ CRP but now  $\tau$ BPA is more than 2 times *faster*. For  $T = 1$ ,  $\tau$ BPA is 4-5 times less accurate than  $\tau$ CFD/ $\tau$ CRP and it is also *slower* than  $\tau$ CFD but *faster* than  $\tau$ CRP. However in aggregate, when both the cases  $T = 0.3$  and 1 are considered,  $\tau$ BPA is 4 (2) times *slower* (*faster*) than  $\tau$ CFD ( $\tau$ CRP) but it is around 4 times more accurate. Similarly on comparing the exact methods we find that eBPA is 6 (2) times *slower* than eCFD (eCRP) but it is also approximately 4 times more accurate.
- Notice from Table 2 that across the board, the standard deviations for the tau-leap estimation methods are not significantly different from their exact counterparts, indicating that tau-leap simulations do not add additional variance to the sensitivity estimators even though they affect the bias. This point is also reinforced by the similarity of the estimator probability distributions in Figure 1(B).

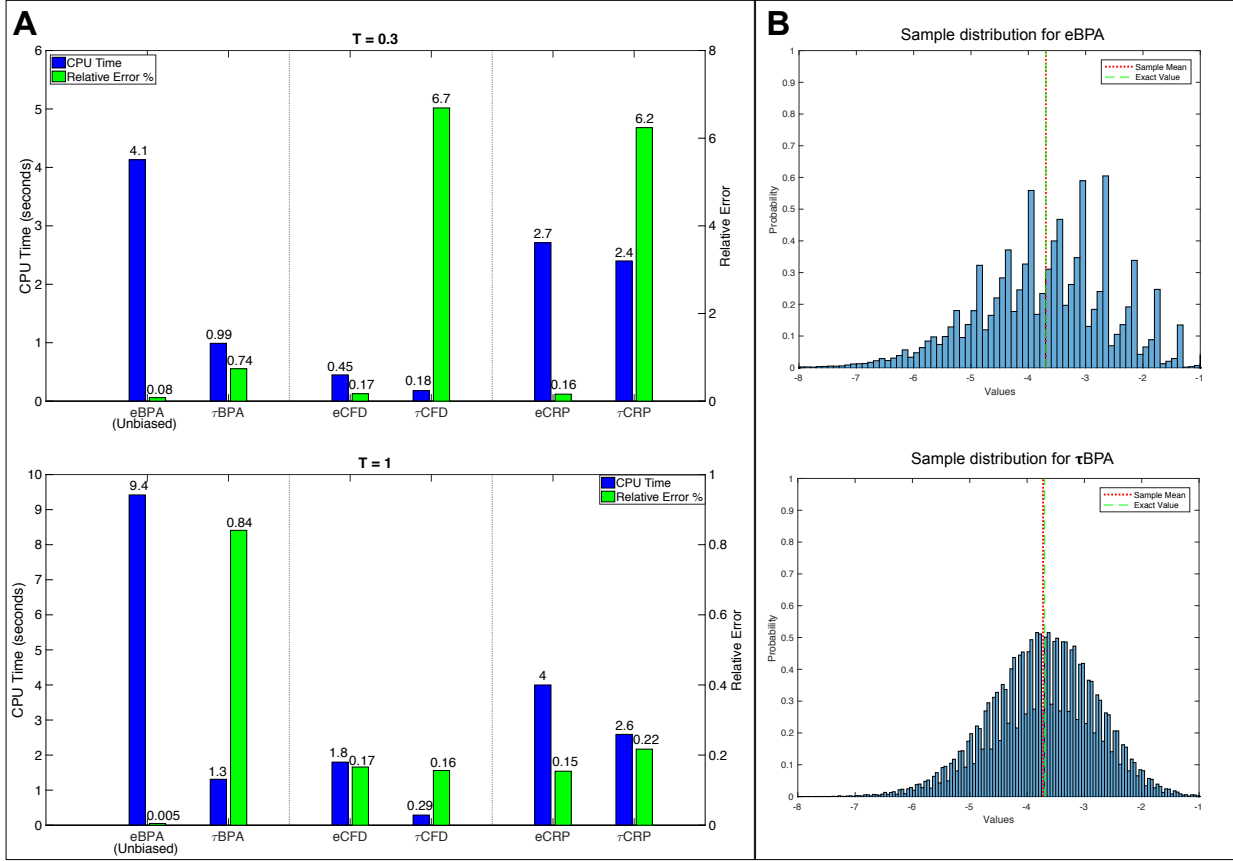
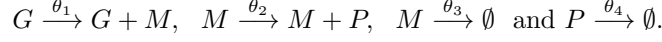


Figure 1: **Birth-death model:** Panel A compares the various sensitivity estimation methods in terms of the CPU Time (calibrated with the *left* y-axis) and the relative error (calibrated with the *right* y-axis). The sensitivities are estimated for  $T = 0.3$  and 1 using  $N = 10^5$  samples. For the case  $T = 0.3$ , we plot the histograms corresponding to probability distributions of the estimator random variables for eBPA and  $\tau$ BPA in panel B. The sample mean and the exact sensitivity value are also indicated.

## 4.2 Gene Expression Network

Our second example considers the model for gene expression given in [43]. It has three species : Gene ( $G$ ), mRNA ( $M$ ) and protein ( $P$ ), and there are four reactions given by



The rate of translation of a gene into mRNA is  $\theta_1$  while the rate of transcription of mRNA into protein is  $\theta_2$ . The degradation of mRNA and protein molecules occurs at rates  $\theta_3$  and  $\theta_4$  respectively. Typically  $\theta_3 \gg \theta_4$  implying that a protein molecule lives much longer than a mRNA molecule. We set  $\theta_1 = 60$ ,  $\theta_2 = 100$ ,  $\theta_3 = 3$  and  $\theta_4 = 0.1$ . Let  $(X(t))_{t \geq 0}$  be the  $\mathbb{N}_0^2$ -valued Markov process representing the reaction dynamics. For any time  $t$ ,  $X(t) = (X_1(t), X_2(t))$ , where  $X_1(t)$  and  $X_2(t)$  are the number of mRNA and protein molecules respectively. We assume that  $(X_1(0), X_2(0)) = (0, 0)$  and define  $f : \mathbb{N}_0^2 \rightarrow \mathbb{R}$  by  $f(x_1, x_2) = x_2$ . At  $T = 1$ , our goal is to estimate

$$S_\theta(f, T) = \partial \mathbb{E}(f(X(T))) = \partial \mathbb{E}(X_2(T)), \quad (4.44)$$

for  $\theta = \theta_3$  and  $\theta = \theta_4$ . These values measure the sensitivity of the mean of the protein population at time  $T = 1$  with respect to the two degradation rates  $\theta_3$  and  $\theta_4$ .

For each  $\theta = \theta_3, \theta_4$  we estimate the sensitivity using all the six methods and the estimator means and standard deviations are presented in Table 3. Like the birth-death example, for this network we can also compute the sensitivity exactly and the values are provided in the caption of Table 3. With these values we can compute the relative errors (4.43). These errors along with the CPU times are compared for all the methods in Figure 2. The results are largely consistent with the observations we made for the birth-death example. Considering both the cases  $\theta = \theta_3$  and  $\theta_4$ ,  $\tau$ BPA is 4.9 (1.1) times slower than  $\tau$ CFD ( $\tau$ CRP) but it is also around 1.3 times more accurate than both  $\tau$ CFD and  $\tau$ CRP. Notice that in this example the additive effect of the two sources of bias (finite-difference and tau-leap approximations) in  $\tau$ CFD/ $\tau$ CRP can be readily seen for both the cases  $\theta = \theta_3, \theta_4$ .

	eBPA		eCFD		eCRP	
$\theta$	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
$\theta_3$	-269.404	0.3978	-268.728	0.8081	-268.649	0.2367
$\theta_4$	-514.829	0.5983	-515.59	0.3841	-515.82	0.3875
	$\tau$ BPA		$\tau$ CFD		$\tau$ CRP	
$\theta$	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
$\theta_3$	-303.901	0.3314	-255.958	0.8083	-256.325	0.7205
$\theta_4$	-498.69	0.3435	-432.21	0.3377	-431.43	0.2926

Table 3: **Gene Expression Network:** Sensitivity estimation results for  $\theta = \theta_3, \theta_4$ . For all the methods, the estimator mean (2.6) and standard deviation (2.8) are mentioned for  $N = 10^5$ . The exact sensitivity values are  $-268.848$  for  $\theta = \theta_3$  and  $-515.084$  for  $\theta = \theta_4$ .

## 4.3 Genetic toggle switch

As our last example we look at a simple network with nonlinear propensity functions. Consider the network of a genetic toggle switch proposed by Gardner et. al. [16]. This network has two species  $\mathcal{U}$  and  $\mathcal{V}$  that interact through the following four reactions



where the propensity functions  $\lambda_i$ -s are given by

$$\lambda_1(x_1, x_2) = \frac{\alpha_1}{1 + x_2^\beta}, \quad \lambda_2(x_1, x_2) = x_1, \quad \lambda_3(x_1, x_2) = \frac{\alpha_2}{1 + x_1^\gamma} \quad \text{and} \quad \lambda_4(x_1, x_2) = x_2.$$



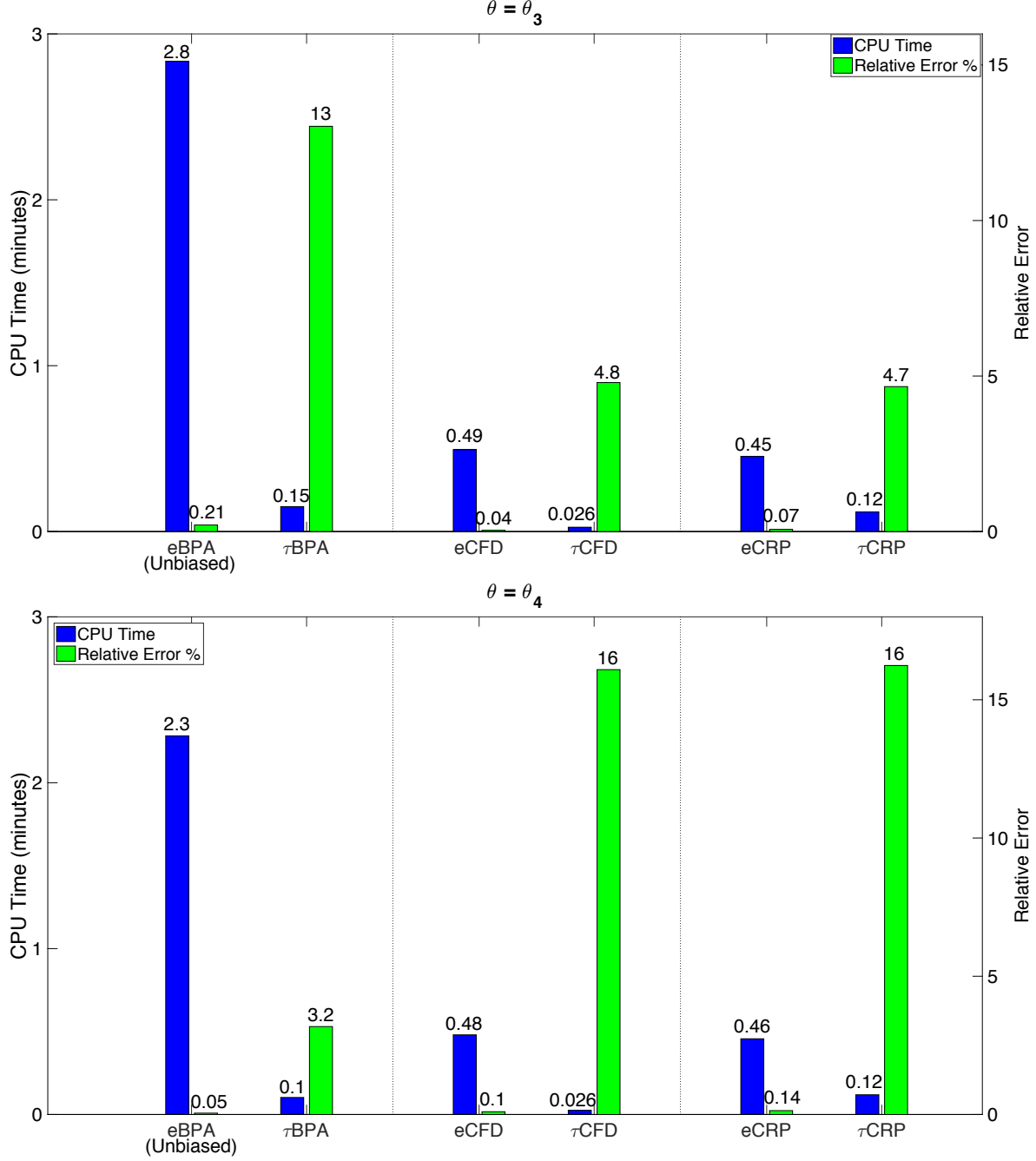


Figure 2: **Gene Expression Network:** This figure compares the various sensitivity estimation methods in terms of the CPU Time (calibrated with the *left* y-axis) and the relative error (calibrated with the *right* y-axis). The sensitivities are estimated for  $\theta = \theta_3$  and  $\theta_4$  using  $N = 10^5$  samples.

In the above expressions,  $x_1$  and  $x_2$  denote the number of molecules of  $\mathcal{U}$  and  $\mathcal{V}$  respectively. We set  $\alpha_1 = 50$ ,  $\alpha_2 = 16$ ,  $\beta = 2.5$  and  $\gamma = 1$ . Let  $(X(t))_{t \geq 0}$  be the  $\mathbb{N}_0^2$ -valued Markov process representing the reaction dynamics with initial state  $(X_1(0), X_2(0)) = (0, 0)$ . For  $T = 0.5$  and  $f(x) = x_1$ , our goal is to estimate

$$S_\theta(f, T) = \partial \mathbb{E}(f(X(T))) = \partial \mathbb{E}(X_1(T)),$$

for  $\theta = \alpha_1, \alpha_2, \beta$  and  $\gamma$ . In other words, we would like to measure the sensitivity of the mean of the number of  $\mathcal{U}$  molecules at time  $T = 10$ , with respect to all the model parameters. We estimate these sensitivities with all the six methods and the results are presented in Table 4 and Figure 3.

In this example, we cannot compute the sensitivity values exactly because of nonlinearity of the propensity functions. So we obtain accurate approximations of these using the unbiased estimator (eBPA) with a large sample size ( $N = 10^6$ ). These approximate values are given in the caption of Table 4 and they were used in computing the relative errors (4.43) for Figure 3. The observations are similar to the previous two examples, but here the tau-leap estimators perform poorly in terms of accuracy, possibly due to nonlinearities in the propensity functions. Considering all the four parameters  $\theta = \alpha_1, \alpha_2, \beta$  and  $\gamma$ ,  $\tau$ BPA is 6 (2.1) times *slower* (*faster*) than  $\tau$ CFD ( $\tau$ CRP) and it is 1.9 (1.8) times more accurate. Similarly comparison among the exact methods reveal that eBPA is 4.9 (1.4) times *slower* (*faster*) than eCFD (eCRP) and it is 5.8 (2.6) times more accurate. Again the additive nature of the two sources of bias (finite-difference and tau-leap approximations) in  $\tau$ CFD/ $\tau$ CRP is clearly visible for all the parameters.

	eBPA		eCFD		eCRP	
$\theta$	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
$\alpha_1$	0.3266	0.0007	0.3185	0.01	0.3215	0.0071
$\alpha_2$	-0.3946	0.0008	-0.3864	0.0175	-0.4012	0.0079
$\beta$	-0.3828	0.002	-0.3732	0.0077	-0.3884	0.0076
$\gamma$	3.9449	0.008	3.9782	0.0513	3.9635	0.0326
	$\tau$ BPA		$\tau$ CFD		$\tau$ CRP	
$\theta$	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
$\alpha_1$	0.3148	0.0008	0.2891	0.0087	0.2811	0.0081
$\alpha_2$	-0.3576	0.0007	-0.4193	0.0182	-0.4223	0.0168
$\beta$	-0.4771	0.002	-0.5142	0.0084	-0.491	0.0079
$\gamma$	3.7999	0.0075	2.8915	0.0406	2.9262	0.0385

Table 4: **Genetic toggle switch:** Sensitivity estimation results w.r.t. all the model parameters  $\alpha_1, \alpha_2, \beta$  and  $\gamma$ . For all the methods, the estimator mean (2.6) and standard deviation (2.8) are mentioned for  $N = 10^5$ . The exact sensitivity values are approximately 0.3272 for  $\theta = \alpha_1$ , -0.3963 for  $\theta = \alpha_1$ , -0.3854 for  $\theta = \beta$  and 3.9541 for  $\theta = \gamma$ .

## 5 Conclusions and future work

Estimation of parameter sensitivities for stochastic reaction networks is an important and difficult problem. The main source of difficulty is that all the estimation methods rely on exact simulations of the reaction dynamics performed using Gillespie’s SSA [18] or its variants [17, 4]. It is well-known that these simulation algorithms are computationally very demanding as they track each and every reaction event which can be very cumbersome. This issue represents the main bottleneck in the use of sensitivity analysis for systems modeled as stochastic reaction networks. The aim of this paper is to develop a method, called *Tau Bernoulli Path Algorithm* ( $\tau$ BPA), that feasibly deals with this issue by requiring only approximate tau-leap simulations of the reaction dynamics, and still providing provably accurate estimates for the sensitivity values. This method is based on an explicit integral representation for parameter sensitivity that was derived from the formula given in [25]. Furthermore, by replacing the tau-leap simulation scheme in  $\tau$ BPA with an exact simulation scheme like SSA, we obtain a new unbiased method (called eBPA) for sensitivity estimation, that can serve as the natural limit of  $\tau$ BPA when the step-size  $\tau$  gets smaller and smaller.

Using computational examples we compare  $\tau$ BPA with our proposed tau-leap versions of the finite-difference schemes [2, 40] that are commonly employed for sensitivity estimation. We find that even though  $\tau$ BPA is typically *slower* than these tau-leap finite-difference schemes, it is usually more accurate. This is primarily because the two sources of bias (finite-difference and tau-leap approximations) often pile on top of each other, thereby compromising the accuracy of an estimate. This makes  $\tau$ BPA an appealing

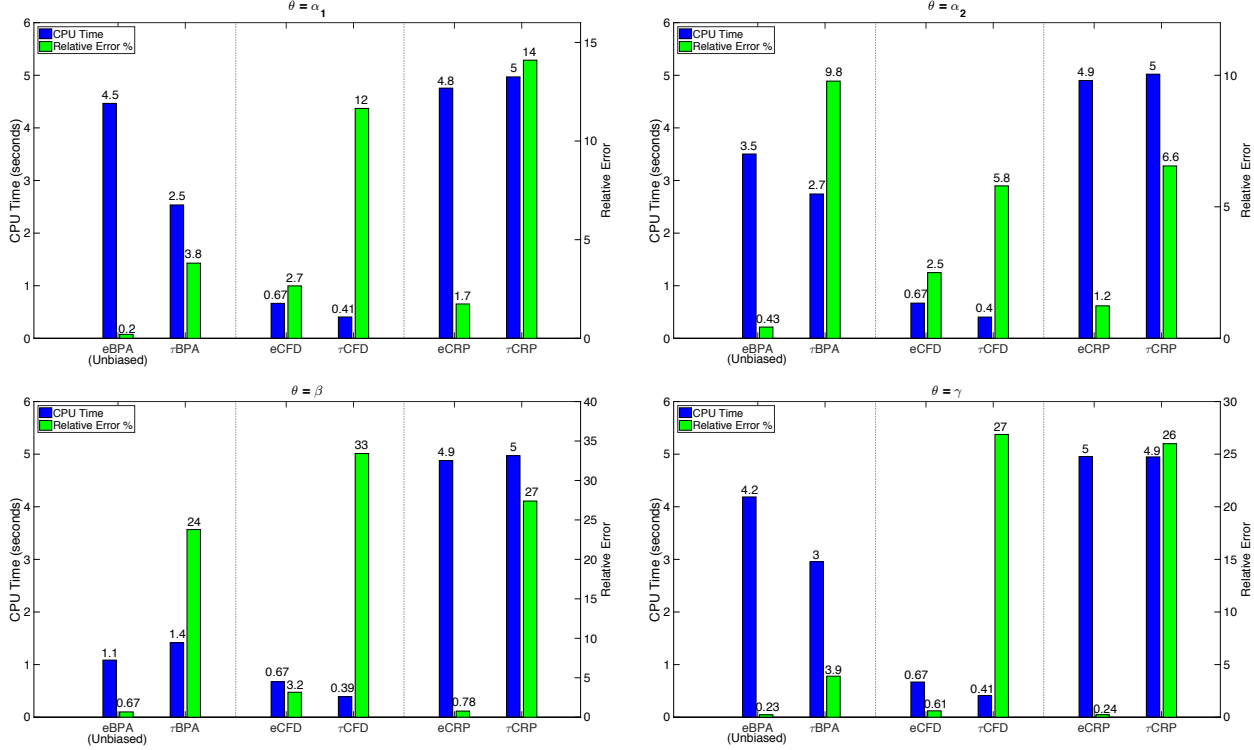


Figure 3: **Genetic toggle switch:** This figure compares the various sensitivity estimation methods in terms of the CPU Time (calibrated with the *left* y-axis) and the relative error (calibrated with the *right* y-axis). The sensitivities are estimated for  $\theta = \alpha_1, \alpha_2, \beta$  and  $\gamma$  using  $N = 10^5$  samples.

method for sensitivity analysis of stochastic reaction networks, where the exact dynamical simulations are computationally infeasible and tau-leap approximations become necessary.

As we argue in Section 2.3, tau-leap simulations provide a natural way to *trade-off* estimator bias with gains in computational speed. Therefore it would be of fundamental importance to extend the ideas in this paper and try to *maximize* the computational gains from tau-leap simulations while sacrificing the *minimum* amount of accuracy. In this context, we now mention two possible directions for future research. The method we proposed here,  $\tau$ BPA, can work with any underlying tau-leap simulation scheme, but for simplicity we examined it with the most basic tau-leap scheme i.e. an explicit Euler method with a constant (deterministic) step-size and Poissonian reaction firings [19]. As this tau-leap scheme has several drawbacks (see [20]), it is very likely that  $\tau$ BPA can yield much better results if a more sophisticated tau-leap scheme is employed, possibly with random step-sizes [11, 5, 31], or with Binomial leaps [44] or using implicit step-size selection [36]. We shall explore these issues in a future paper. Another promising direction would be to devise a *multilevel* version of  $\tau$ BPA, where estimators are constructed for a range to  $\tau$ -values, and are suitably coupled to simultaneously reduce the overall estimator's bias and variance [7, 29, 31].

## Appendix

In this section we provide the proofs of the main results in this paper, namely, Theorems 3.1 and 3.3.

**Proof.**[Proof of Theorem 3.1] Let  $\{\mathcal{F}_t\}$  be the filtration generated by the process  $(X_\theta(t))_{t \geq 0}$  and let  $\sigma_i$  be its  $i$ -th jump time for  $i = 1, 2, \dots$ . We define  $\sigma_0 = 0$  for convenience. Since the process  $(X_\theta(t))_{t \geq 0}$  is constant

between consecutive jump times we can write

$$\begin{aligned}
& \mathbb{E} \left( \int_0^T \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(t)) dt \right) \\
&= \sum_{i=0}^{\infty} \mathbb{E} \left( \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(\sigma_i)) (\sigma_{i+1} \wedge T - \sigma_i \wedge T) \right) \\
&= \sum_{i=0}^{\infty} \mathbb{E} \left( \mathbb{E} \left( \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(\sigma_i)) (\sigma_{i+1} \wedge T - \sigma_i \wedge T) \middle| \mathcal{F}_{\sigma_i} \right) \right) \\
&= \sum_{i=0}^{\infty} \mathbb{E} \left( \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(\sigma_i)) \mathbb{E}((\sigma_{i+1} \wedge T - \sigma_i \wedge T) | \mathcal{F}_{\sigma_i}) \right) \\
&= \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^{\infty} \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} (f(X_\theta(\sigma_i) + \zeta_k) - f(X_\theta(\sigma_i))) \mathbb{E}(\delta_i | \mathcal{F}_{\sigma_i}, \sigma_i < T) \right), \tag{5.45}
\end{aligned}$$

where  $\delta_i = \sigma_{i+1} \wedge T - \sigma_i \wedge T$  and the last equality holds due to linearity of the expectation operator and the fact that  $\delta_i = 0$  if  $\sigma_i \geq T$ . Given  $X_\theta(\sigma_i) = y$  and  $\sigma_i = u < T$ , the distribution of the random variable  $\delta_i$  has the *cumulative density function* given by

$$\mathbb{P}(\delta_i < s | X_\theta(\sigma_i) = y, \sigma_i = u) = \begin{cases} 0 & \text{if } s < 0 \\ 1 - e^{-\lambda_0(y, \theta)s} & \text{if } 0 \leq s < (T - u) \\ 1 & \text{if } s \geq (T - u). \end{cases}$$

This shows that for any continuous function  $g : [0, \infty) \rightarrow [0, \infty)$  we have

$$\begin{aligned}
\mathbb{E} \left( \int_0^{\delta_i} g(s) ds \middle| X_\theta(\sigma_i) = y, \sigma_i = u \right) &= \mathbb{P}(\delta_i \geq (T - u) | X_\theta(\sigma_i) = y, \sigma_i = u) \int_0^{T-u} g(s) ds \\
&+ \mathbb{E} \left( \mathbb{1}_{\{0 \leq \delta_i < (T-u)\}} \int_0^{\delta_i} g(s) ds \middle| X_\theta(\sigma_i) = y, \sigma_i = u \right) \\
&= e^{-\lambda_0(y, \theta)(T-u)} \int_0^{T-u} g(s) ds \\
&+ \int_0^{T-u} \lambda_0(y, \theta) e^{-\lambda_0(y, \theta)s} \left( \int_0^s g(t) dt \right) ds. \tag{5.46}
\end{aligned}$$

However using integration by parts we get

$$\begin{aligned}
\int_0^{T-u} \lambda_0(y, \theta) e^{-\lambda_0(y, \theta)s} \left( \int_0^s g(t) dt \right) ds &= \left[ -e^{-\lambda_0(y, \theta)s} \left( \int_0^s g(t) dt \right) \right]_{s=0}^{s=T-u} + \int_0^{T-u} e^{-\lambda_0(y, \theta)s} g(s) ds \\
&= -e^{-\lambda_0(y, \theta)(T-u)} \int_0^{T-u} g(s) ds + \int_0^{T-u} e^{-\lambda_0(y, \theta)s} g(s) ds.
\end{aligned}$$

Substituting this expression in equation (5.46) we get

$$\mathbb{E} \left( \int_0^{\delta_i} g(s) ds \middle| X_\theta(\sigma_i) = y, \sigma_i = u \right) = \int_0^{T-u} e^{-\lambda_0(y, \theta)s} g(s) ds. \tag{5.47}$$

Taking  $g(s) = 1$  for all  $s$  gives us

$$\mathbb{E}(\delta_i | X_\theta(\sigma_i) = y, \sigma_i = u) = \int_0^{T-u} e^{-\lambda_0(y, \theta)s} ds = \int_0^{T-u} e^{-\lambda_0(y, \theta)(T-u-s)} ds.$$

Therefore

$$\mathbb{E}(\delta_i | \mathcal{F}_{\sigma_i}, \sigma_i < T) = \int_0^{T-\sigma_i} e^{-\lambda_0(X_\theta(\sigma_i), \theta)(T-\sigma_i-s)} ds$$

and equation (5.45) implies that

$$\begin{aligned} & \mathbb{E} \left( \int_0^T \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(t)) dt \right) \\ &= \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(\sigma_i)) \int_0^{T-\sigma_i} e^{-\lambda_0(X_\theta(\sigma_i), \theta)(T-\sigma_i-s)} ds \right). \end{aligned} \quad (5.48)$$

We mentioned in Section 2.2 that the sensitivity value  $S_\theta(f, T)$  can be expressed as the expectation of the random variable  $s_\theta(f, T)$  defined by (2.16). Using this fact along with (5.48) we obtain

$$\begin{aligned} S_\theta(f, T) &= \sum_{k=1}^K \mathbb{E} \left( \int_0^T \frac{\partial \lambda_k(X_\theta(t), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(t)) dt \right) + \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} R_\theta(X_\theta(\sigma_i), f, T - \sigma_i, k) \right) \\ &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \Delta_{\zeta_k} f(X_\theta(\sigma_i)) \int_0^{T-\sigma_i} e^{-\lambda_0(X_\theta(\sigma_i), \theta)(T-\sigma_i-s)} ds \right) \\ &\quad + \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} R_\theta(X_\theta(\sigma_i), f, T - \sigma_i, k) \right) \\ &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \left( R_\theta(X_\theta(\sigma_i), f, T - \sigma_i, k) \right. \right. \\ &\quad \left. \left. + \Delta_{\zeta_k} f(X_\theta(\sigma_i)) \int_0^{T-\sigma_i} e^{-\lambda_0(X_\theta(\sigma_i), \theta)(T-\sigma_i-s)} ds \right) \right). \end{aligned}$$

Since  $R_\theta$  is given by (2.15) we have

$$\begin{aligned} S_\theta(f, T) &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0: \sigma_i < T}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \int_0^{T-\sigma_i} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, s) e^{-\lambda_0(X_\theta(\sigma_i), \theta)(T-\sigma_i-s)} ds \right) \\ &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0}^\infty \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \int_0^{T-\sigma_i \wedge T} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s) e^{-\lambda_0(X_\theta(\sigma_i), \theta)s} ds \right). \end{aligned} \quad (5.49)$$

Relation (5.47) with  $g(s) = \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s)$  shows that given  $X_\theta(\sigma_i) = y$  and  $\sigma_i = u < T$ , the following holds

$$\begin{aligned} & \int_0^{T-u} \Delta_{\zeta_k} \Psi_\theta(y, f, T - u - s) e^{-\lambda_0(y, \theta)s} ds \\ &= \mathbb{E} \left( \int_0^{\delta_i} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s) ds \middle| X_\theta(\sigma_i) = y, \sigma_i = u \right) \\ &= \mathbb{E} \left( \int_0^{\sigma_{i+1} \wedge T - \sigma_i \wedge T} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s) ds \middle| X_\theta(\sigma_i) = y, \sigma_i = u \right) \\ &= \mathbb{E} \left( \int_{\sigma_i \wedge T}^{\sigma_{i+1} \wedge T} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T - s) ds \middle| X_\theta(\sigma_i) = y, \sigma_i = u \right) \end{aligned}$$

Therefore

$$\frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \int_0^{T-\sigma_i \wedge T} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T - \sigma_i - s) e^{-\lambda_0(X_\theta(\sigma_i), \theta)s} ds$$

$$\begin{aligned}
&= \frac{\partial \lambda_k(X_\theta(\sigma_i), \theta)}{\partial \theta} \mathbb{E} \left( \int_{\sigma_i \wedge T}^{\sigma_{i+1} \wedge T} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T-s) ds \middle| \mathcal{F}_{\sigma_i} \right) \\
&= \mathbb{E} \left( \int_{\sigma_i \wedge T}^{\sigma_{i+1} \wedge T} \frac{\partial \lambda_k(X_\theta(s), \theta)}{\partial \theta} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T-s) ds \middle| \mathcal{F}_{\sigma_i} \right)
\end{aligned}$$

since  $X_\theta(s) = X_\theta(\sigma_i)$  for all  $s \in [\sigma_i, \sigma_{i+1})$ . Substituting this expression in (5.49) implies that

$$\begin{aligned}
S_\theta(f, T) &= \sum_{k=1}^K \mathbb{E} \left( \sum_{i=0}^{\infty} \mathbb{E} \left( \int_{\sigma_i \wedge T}^{\sigma_{i+1} \wedge T} \frac{\partial \lambda_k(X_\theta(s), \theta)}{\partial \theta} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T-s) ds \middle| \mathcal{F}_{\sigma_i} \right) \right) \\
&= \sum_{k=1}^K \sum_{i=0}^{\infty} \mathbb{E} \left( \mathbb{E} \left( \int_{\sigma_i \wedge T}^{\sigma_{i+1} \wedge T} \frac{\partial \lambda_k(X_\theta(s), \theta)}{\partial \theta} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T-s) ds \middle| \mathcal{F}_{\sigma_i} \right) \right) \\
&= \sum_{k=1}^K \sum_{i=0}^{\infty} \mathbb{E} \left( \int_{\sigma_i \wedge T}^{\sigma_{i+1} \wedge T} \frac{\partial \lambda_k(X_\theta(s), \theta)}{\partial \theta} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T-s) ds \right) \\
&= \sum_{k=1}^K \mathbb{E} \left( \int_0^T \frac{\partial \lambda_k(X_\theta(s), \theta)}{\partial \theta} \Delta_{\zeta_k} \Psi_\theta(X_\theta(\sigma_i), f, T-s) ds \right).
\end{aligned}$$

This completes the proof of this result.  $\square$

**Proof.**[Proof of Theorem 3.3] For each  $k = 1, \dots, K$  define  $g_k, h_k$  by

$$\begin{aligned}
g_k(x, t) &= \partial \lambda_k(x) (\Psi(x + \zeta_k, f, T-t) - \Psi(x, f, T-t)) \\
h_k(x, t) &= \partial \lambda_k(x) (\tilde{\Psi}_{\alpha_1, \beta_1(t)}(x + \zeta_k, f, T-t) - \tilde{\Psi}_{\alpha_1, \beta_1(t)}(x, f, T-t)).
\end{aligned} \tag{5.50}$$

Without loss of generality, we can assume that there exists a  $C > 0$  such that

$$\max\{\partial \lambda_k(x), f(x) | k = 1, \dots, K\} \leq C(1 + \|x\|^p), \forall x \in \mathbb{N}_0^d.$$

Then due to Lemma 2.2 we obtain

$$\begin{aligned}
\sup_{t \in [0, T]} |h_k(x, t) - g_k(x, t)| &\leq \partial \lambda_k(x) C C_1(p, T, \alpha_1) \left( (1 + \|x\|^{\xi(p)}) + (1 + \|x + \zeta_k\|^{\xi(p)}) \right) \tau_{\max}^\gamma \\
&\leq C^2 C_1(p, T, \alpha_1) (1 + \|x\|^p) \left( (1 + \|x\|^{\xi(p)}) + (1 + \|x + \zeta_k\|^{\xi(p)}) \right) \tau_{\max}^\gamma \\
&\leq c_0(p) C^2 C_1(p, T, \alpha_1) \left( 1 + \|x\|^{(p+\xi(p))} \right) \tau_{\max}^\gamma,
\end{aligned} \tag{5.51}$$

where  $c_0(p)$  is a constant that depends only on  $p$  as well as  $\zeta_1, \dots, \zeta_K$ . Lemma 2.2 also shows that

$$\begin{aligned}
\sup_{t \in [0, T]} |h_k(x, t)| &\leq \partial \lambda_k(x) C C_3(p, T, \alpha_1) ((1 + \|x\|^p) + (1 + \|x + \zeta_k\|^p)) \\
&\leq c_1(p) C^2 C_3(p, T, \alpha_1) (1 + \|x\|^{2p})
\end{aligned} \tag{5.52}$$

and

$$\sup_{t \in [0, T]} |g_k(x, t)| \leq c_1(p) C^2 C_2(p, T) (1 + \|x\|^{2p}), \tag{5.53}$$

where  $c_1(p)$  is again a constant that depends only on  $p$  and  $\zeta_1, \dots, \zeta_K$ .

From (5.52) and Lemma 2.2 it follows that

$$\sup_{t \in [0, T]} |\mathbb{E}(h_k(Z_{\alpha_0, \beta_0}(x_0, t), t)) - \mathbb{E}(h_k(X(t), t))| \leq c_1(p) C^2 C_3(p, T, \alpha_1) C_1(2p, T, \alpha_0) \left( 1 + \|x_0\|^{\xi(2p)} \right) \tau_{\max}^\gamma. \tag{5.54}$$

Moreover from (5.51), we get

$$\mathbb{E}(|h_k(X(t), t) - g_k(X(t), t)|) \leq c_0(p) C^2 C_1(p, T, \alpha_1) (1 + \mathbb{E}(\|X(t)\|^{(p+\xi(p))})) \tau_{\max}^\gamma,$$



and hence using Assumption 2, we obtain

$$\sup_{t \in [0, T]} \mathbb{E}(|h_k(X(t), t) - g_k(X(t), t)|) \leq c_0(p)C^2C_1(p, T, \alpha_1)C_2(p + \xi(p), T) \left(1 + \|x_0\|^{p+\xi(p)}\right) \tau_{\max}^\gamma. \quad (5.55)$$

Note that

$$\begin{aligned} \left| \tilde{S}(f, T) - S(f, T) \right| &= \left| \sum_{k=1}^K \int_0^T (\mathbb{E}(h_k(Z_{\alpha_0, \beta_0}(x_0, t), t)) - \mathbb{E}(g_k(X(t), t))) dt \right| \\ &\leq \sum_{k=1}^K \left| \int_0^T \mathbb{E}(h_k(Z_{\alpha_0, \beta_0}(x_0, t), t)) dt - \int_0^T \mathbb{E}(g_k(X(t), t)) dt \right| \\ &\leq \sum_{k=1}^K \int_0^T |\mathbb{E}(h_k(Z_{\alpha_0, \beta_0}(x_0, t), t)) - \mathbb{E}(h_k(X(t), t))| dt \\ &\quad + \sum_{k=1}^K \int_0^T |\mathbb{E}(h_k(X(t), t)) - \mathbb{E}(g_k(X(t), t))| dt. \end{aligned}$$

Using (5.54) and (5.55) we obtain the bound

$$\begin{aligned} \left| \tilde{S}(f, T) - S(f, T) \right| &\leq KTc_1(p)C^2C_3(p, T, \alpha_1)C_1(2p, T, \alpha_0) \left(1 + \|x_0\|^{\xi(2p)}\right) \tau_{\max}^\gamma \\ &\quad + KTc_0(p)C^2C_1(p, T, \alpha_1)C_2(p + \xi(p), T) \left(1 + \|x_0\|^{p+\xi(p)}\right) \tau_{\max}^\gamma, \end{aligned}$$

which proves the theorem.  $\square$

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